Hormone Therapy in Practice

Authors and Publishers

Schering A.G. Berlin

Revised and enlarged second edition



Medical and Scientific Publications

Erich Blaschker, Berlin

Foreword to the Second Edition

It is almost impossible to carry the torch of truth through a crowd without singeing someone's beard.
Georg Christoph Lichtenberg

Scientific knowledge of the nature and effects of hormones and their therapeutic use is in such an upsurge that it was necessary already two years after the appearance of the first edition to enlarge the new edition and to subject it to a thorough revision There are new sections on the adrenocorticotropic hormone (ACTH) and the thyrotropic hormone of the anterior pituitary. Some of the illustrations have been replaced by others or altered in accordance with scientific advances. The bibliography, which goes up to 31 December 1952, has been increased by 403 entries. For this reason, it should be particularly welcome to the medical scientific worker. The subject index has been correspondingly enlarged considerably.

We gratefully acknowledge the numerous and valuable suggestions made to us by readers

The enlargement undertaken in this edition, and the lively interest shown in the first edition of "Hormone Therapy in Practice," justify to follow the wishes of the publishing trade for a new edition and also for a translation of the book into foreign languages. The English translation has eventually been concluded after tedious and extensive preparations and now been given to print.

SCHERING A.G.

Berlin, April 1954

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Introduction

Knowledge accumulated over the centuries about the significance of the glands of internal secretion stimulated many physicians, physiologists, pharmacologists and chemists to intense experimental and clinical research. It was noted as early as 1849 that the consequences of castration in the cock remained absent if the removed testes were reimplanted at another site in the body [1]. Seven years later, because of the previously described clinical picture of Addison's disease [2], the fact that the adrenals are essential to life was recognized [3]. Thus began the development of modern endocrinology, given a further impetus by the observation of the "rejuvenating" effect of injections of animal testicular extracts. Further studies showed that the loss of function due to the removal of the thyroid gland led to the clinical picture of myxoedema. On the other hand, it was recognized that Graves's disease could be improved by partial removal of the goitre, and must therefore depend upon overfunction of the thyroid [4]. More systematic research confirmed the internal secretory nature of the pituitary and the pancreas [5, 6] Research now made rapid progress, being greatly helped by the preparation of various hormones in pure form. Hormone research received its greatest impulse finally by the discovery of the sex hormones, on which some famous scientists who are still active worked [7, 8 9, 10, 11, 12 etc.] The Schering A. G. of Berlin played a considerable part in the results of modern hormone research and

synthesis [13, 14, 15, 16, 17, 18, 19, 20]. This book reviews the fruits of decades of work and study, of clinical experience and successes in hormone therapy. Because of its small compass, it lays no claim to completeness, and confines itself to the most important fields in endocrinology, the steroid hormones and the known active agents of the pituitary.

Chemistry, Physiology and Pharmacology

General

The aetiology and treatment of functional disturbances of internal secretion have continued to grow in interest during recent years. Successful treatment of these manifestations is however only possible when the therapist is quite clear about the chemical, physiological and pharmacological properties and effects of the hormones. An exact knowledge of the effects of hormones is more necessary than is the case with the other drugs used in medicine, since they are not to be compared with other common drugs; as endogenous active agents with many and often contrary effects, they represent something basically different. In addition to substitution treatment, they make symptomatic and often even causal therapy possible. As the most recent results of research and treatment show, the nature and mode of action of hormones are by no means completely known and clinically tested. Ceaseless work will still be necessary in the future if further success is to be obtained in the fields already opened up

The causes of endocrine disturbances may lie in congenital and acquired "disharmonies." Physical and mental stress, toxins, infective-toxic influences, morbid anatomical changes, the environment, diet and many other factors may lead to disturbances in the endocrine regulation of vital processes. In this the closest relationships are maintained between the endocrine, autonomic nervous and central nervous systems. It is self-evident that before treatment is begun, the patient must be investigated thoroughly. Both deficiency and excess of hormones in the body may lead to a disturbance of physiological vital processes. Nerv-

ous stimuli may cause endocrine reactions; convers influence the nervous system.

In addition to other agents, the hormones dominate function of cells and tissues and generative an processes. Either the function of certain organs is the collaboration of several *hormones of different o* in the same direction, or different effects necessa physiological march of vital processes are achieved a organ by various hormones formed in a single gland. ' icance and results of this collective action of all the glands are apparent from the fact that mental and development depend upon the normal functioning o glands rather than of a single one. The mechanism of c interaction illustrated in Figure 1 is definitely more com than can be shown in a diagram. Moreover these p have not been completely clarified as yet. However, tl itary plays a leading part. From this gland, neural and en humoral connexions run to the hypothalamus, central r system *and other endocrine glands*. *The whole system* a functional unit. It is disturbed if there is an interrupt only one place, whatever the cause [21, 22], such a distu may remain localized or have a generalized effect.

The *various phases of life* – childhood, youth, adult life, n age and old age – correspond to different hormone levels, v *determine and assure* interplay and normal course of the processes and reactions typical of that phase. Disturbance these normal glandular and hormonal correlations manifest tl selves by symptoms which must be regarded as pathological.

Hence the hormones are indispensable for the normal con of vital processes. They transmit the psychological and phys logical unity of the personality.

Apart from the hormones formed in the glands and therefore known as glandular, there are also aglandular tissue hormones [23]. These are formed in the body tissues, and their *presence is*

ous stimuli may cause endocrine reactions; conversely, hormones influence the nervous system.

In addition to other agents, the hormones dominate metabolism, function of cells and tissues and generative and functional processes. Either the function of certain organs is affected by the collaboration of several hormones of different origin, acting in the same direction, or different effects necessary for the physiological march of vital processes are achieved at the end-organ by various hormones formed in a single gland. The significance and results of this collective action of all the endocrine glands are apparent from the fact that mental and physical development depend upon the normal functioning of several glands rather than of a single one. The mechanism of endocrine interaction illustrated in Figure 1 is definitely more complicated than can be shown in a diagram. Moreover these processes have not been completely clarified as yet. However, the pituitary plays a leading part. From this gland, neural and endocrine-humoral connexions run to the hypothalamus, central nervous system and other endocrine glands. The whole system forms a functional unit. It is disturbed if there is an interruption at only one place, whatever the cause [21, 22]; such a disturbance may remain localized or have a generalized effect

The various phases of life – childhood, youth, adult life, middle age and old age – correspond to different hormone levels, which determine and assure interplay and normal course of the vital processes and reactions typical of that phase Disturbances of these normal glandular and hormonal correlations manifest themselves by symptoms which must be regarded as pathological

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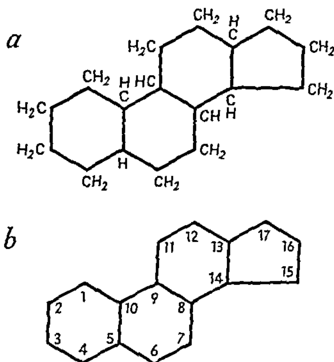
apparently necessary only for the function of these tissues; they are formed, re-destroyed or changed back in the tissues themselves.

Among glandular hormones, we can distinguish chemically between steroid hormones and proteohormones. Recognition of the chemical classification of these hormones was a direct aid to research and made great results in treatment possible. The use of organ preparations and transplants, which had up to then been usual and necessary, now had to give way to better and more exact methods of treatment. It became possible to avoid the unsatisfactory therapeutic results hitherto obtained with organ extracts whose hormone content depended on many factors (see page 16). The preparation of pure hormones opened up new prospects for completely clear-cut methods of treatment under the control of the physician.

The basis for the discovery of chemical and biological properties and for the synthesis of hormones is animal experiment. Removal of certain glands from the body permits the observation of deficiency signs, and attempts can be made to relieve these by feeding or transplanting the same glands, or by injecting extracts of the glands. The next step in research is usually the isolation and determination of the chemical structure of the effective agents and finally their synthesis. Then, on the basis of exact standardization, an individually determined and physiologically adapted hormone therapy can be developed.

The structural formulae of the steroid hormones are now known, and they can therefore be synthesized chemically. Steroids are substances closely related to sterane. The steroid hormones are also derivatives of sterane, i. e. the hydrated four-ring system cyclopentanophenanthrene. The structural formula of sterane shows three hydrated benzene rings and one cyclopentane ring (Fig. 2a). In order to indicate the exact position of individual groups and double bonds in the steroids, the 17 carbon atoms are numbered. In order to facilitate review, however, the C and H

atoms are not designated, only the double bonds and the substituents being given. *Fig. 2b* shows the structural formula of sterane in the usual notation, as employed below. All steroid



Sterane

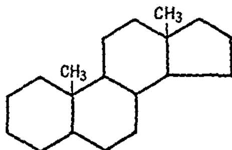
Fig 2

hormones are derived from the basic skeleton of the steroids *(Fig. 3)*.

Male and female sex hormones and also adrenal cortical hormones belong to the steroid hormones. The chemical differences between these hormones depend upon changes in the side-chains, presence or absence of keto and hydroxyl groups in the 3, 11, 16 or 17 position, and single or double bonds at various positions

in the 6-carbon rings. The close chemical relationships of all steroid hormones make it understandable that they often overlap as regards effects, and in some cases may even replace each other. On the other hand, it should be mentioned that trivial changes in chemical structure may cause considerable differences in the direction, intensity and quality of effects.

The sites of origin of the steroid hormones are known, but we do not yet know the nature of the parent substance and the



Basic skeleton of steroids

Fig 3

biochemical processes involved in their formation. Degradation from *sterines* appears possible, but this is as yet unproved [24].

Transformation of hormones into a form suitable for excretion occurs by oxidation and reduction; they are bound to glucuronic acid or sulphuric acid as a *preliminary to excretion in* the urine.

In order to synthesize them chemically, various sterines are used, especially those of animal origin and particularly cholesterol obtained from spinal cords of bovines [15, 20]. The fact that a substance found in the body must be used for synthesis clearly shows the physiological nature of the endogenous hormones so obtained. It also shows the basic difference between these and the exogenous substances also used *in therapy, and* whose oestrogenic properties were discovered by accident. Employment of the latter thus does not constitute true hormone

therapy. They are artificial products not found in the body, and their effects do not correspond in every respect with those of true hormones [25, 26]. Treatment with real hormones is equivalent to *the substitution of naturally occurring agents, and* hence to a physiological action. The synthesis of hormones was important because it had been shown that, apart from the *disadvantages of* use *of* organ extracts mentioned above, *the* amounts of active agents in the latter were so small that they were totally inadequate for successful employment on a large scale. *For* example, to produce from animal organs the amount of oestrogen necessary for inducing a proliferation phase in the endometrium, 10 to 15 kg. of dried powdered pig ovary would be necessary, while from 1 kg. of pig corpus luteum only about 30 to 35 rabbit units of corpus luteum hormone can be obtained. To prepare 1 kg. of crystalline oestradiol 15 to 20 milliard pigs would be required, and $2^1/_2$ million cattle to prepare 1 kg. crystalline desoxycorticosterone [27]. Although the synthesis by steps of hormones takes months and the yield is relatively small, this is the only method of production calculated to put an adequate supply of hormones into the hands of every doctor.

In the course *of time, research turned from the preparation* of substances with a transient action to the production of preparations with a more powerful and a more prolonged effect. Esterification led to an increase in effect and a significant prolongation of action [28, 748]. By hydrating oestrone at the keto group oestradiol was prepared [18], thus increasing endocrine activity fivefold to eightfold. Other advances were the production of tablets for implantation and the introduction of the ethinyl group at the 17 position in the 5-carbon ring [14, 16]. The latter discovery was of particular importance because by means of it *a high-potency endocrine* substance was obtained which is also effective by mouth in tablet form. In contrast to other substances, it is not inactivated by passage through the liver (see page 107).

The hormones of the pituitary, thyroid and parathyroids belong to the group of proteohormones. In contrast to steroid hormones, the structural formulae of the proteohormones are to a large extent still unknown. They are protein compounds of high molecular weight which have so far not been synthesized. Since the yield is very small when anterior pituitary is used as the source of these hormones, they are obtained in part from other sources. Gonadotropic hormones are obtained from pregnant mares' serum and pregnancy urine.

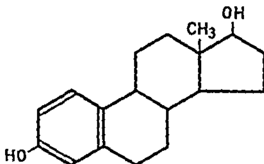
To prepare the gonadotropic hormones the usual methods of protein chemistry are employed. The statements of some research workers that they have been able to separate off follicle-stimulating and luteinizing factors [29, 30] are denied by others [31, 32].

Chemistry, Physiology and Pharmacology of the Female Sex Hormones

The ovary forms two different hormones, follicular hormone or oestrogen and the corpus luteum hormone or progesterone. The site of formation of follicular hormone is the *Graafian* follicle, and that of progesterone the corpus luteum which is *formed out of the Graafian follicle*. During pregnancy, both hormones are produced in relatively large quantity in the placenta as well, this taking over functions of an endocrine gland [33, 34] (see Fig. 18).

The *derivative of follicular hormone* which is excreted in the urine, oestrone (see Fig. 5), was first obtained in a pure state in Germany, where its chemical structure was elucidated [13]. The oestrus hormone oestriol, which also occurs *in pregnancy* urine (see Fig. 6), has three oxygen atoms in the form of hydroxyl *groups (oestrogen* hydrate). By *chemical* transformation of oestrone (hydration of the keto group) oestradiol is produced [18]. This *is the form of* follicular hormone *found in* the ovary itself (see Fig. 4). The effect of the latter is about five to eight times that of the oestrone excreted in the urine. Chemical change and esterification of oestradiol with benzoic acid produced oestradiol benzoate (see Fig. 7), which has a more intense effect *and* a longer duration of action. Finally, the introduction of the ethinyl group at the 17 position in the 5-carbon ring in *oestradiol* gave rise to a preparation which is completely effective by mouth, ethinyl oestradiol (see Fig 8).

The corpus luteum hormone is also derived from sterane. Its chemical *formula* (progesterone) was elucidated in 1934 [35] (see



OESTRADIOL

PROGYNON

(Dragees, drops and implants)

The effective form of follicular hormone in the organism

$C_{18}H_{24}O_2$ Molecular Wt 272 37

Δ 1, 3, 5 (10)-oestratriene—3,17-β - diol

White, odourless crystals, stable in air, slightly soluble in water, but readily soluble in diluted NaOH or KOH, in alcohol, acetone and dioxane, only slightly in plant oils Strongly resistant to acids, bases, heat and digestive enzymes Forms esters with acids, thus intensifying its effect and prolonging its duration of action

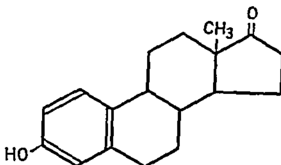
Freezing Pt. 178° C (corrected)

$[\alpha]_D^{20} = + 81°$ C (in alcohol)

Occurrence: follicles, corpus luteum, placenta, urine and germinal glands of male animals, also in the plant world and apart from living things in nature

Fig 4

2*



OESTRONE

The product of follicular hormone excreted in the urine

$C_{18}H_{22}O_2$ Mol Wt 270 36

$\Delta^{1,3,5(10)}$-oestratriene—3-ol-17-one

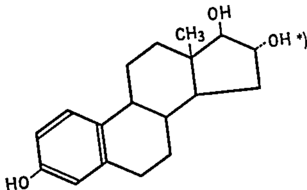
White, odourless crystals, stable in air Insoluble in water Soluble in alcohol, acetone, dioxane, sodium or potassium hydroxide

F Pt 254° C —259° C.

$[\alpha]_D^{20} = +156°$ C (in chloroform)

Occurrence pregnancy urine, urine of pregnant mares and stallions, urine of male subjects, adrenals and placenta of human subjects, testes of the stallion, palm-kernel residues

Fig 5



OESTRIOL

THEELOL (follicular hormone hydrate) Mol Wt 288 37

$C_{18}H_{24}O_3$

Δ 1, 3, 5 (10)-oestratriene—3, 16α, 17β-triol

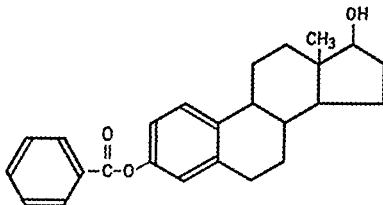
F Pt 280° C

$[\alpha]_D = +66°$ C (in alcohol)

Occurrence Pregnancy urine, human placenta, willow catkin

*) The alpha position of substituents (actually arranged spatially posteriorly) is shown by a dotted line

Fig 6



OESTRADIOL MONOBENZOATE

PROGYNON B oleosum

(Ampoules)

$C_{25}H_{28}O_3$ Mol. Wt 376.47

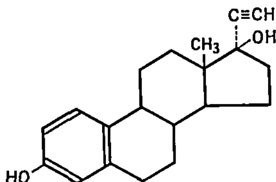
Oestradiol—3-benzoate

White, odourless crystals, stable in air Almost insoluble in water Soluble in alcohol, acetone and dioxane, readily soluble in ether and slightly soluble in vegetable oils

F Pt 192° C —193° C.

$[\alpha]_D^{22} = +60°$ C (Dioxane)

Fig 7



ETHINYL OESTRADIOL

PROGYNON C, PROGYNON M

(Tablets)

$C_{20}H_{24}O_2$ Mol Wt 296 39

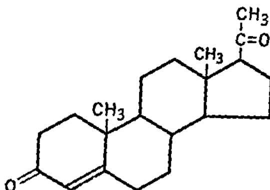
17α-ethinyl-oestradiol

Colourless, fine needles, recrystallizable out of a mixture of equal parts of methanol and water

F Pt = 145° C—146° C

$[\alpha]_D$ = + 1° C (Dioxane)

Fig 8



PROGESTERONE

PROLUTON

(Ampoules and implants)

Corpus luteum hormone

$C_{21}H_{30}O_2$ — Mol Wt 314 4

Δ^4-pregnene—3,20-dione

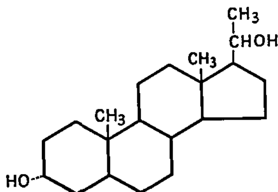
White, odourless crystals, stable in air *Practically insoluble in water Soluble* in alcohol, acetone and dioxane, slightly soluble in vegetable oils It crystallizes out in two polymorphic modifications, and is resistant to acids and heat-stable

F Pt = 128 5° C (rhombic form)
121° C—122° C (*needle form*)

$[\alpha]_D^{20}$ = + 201° C (*chloroform*)

O c c u r r e n c e · corpus luteum, placenta *adrenal cortex*

Fig 9



PREGNANDIOL

Urinary excretory product of progesterone and of the adrenal cortical hormone, desoxycorticosterone

$C_{21}H_{36}O_2$ Mol Wt 320 50

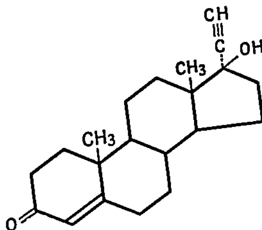
Pregnane—3α, 20a-diol

Crystalline plates belonging to the rhombic system

F Pt = 244° C

Occurrence In the urine in the form of its glucuronide

Fig 10



PREGNENINOLONE

PROLUTON C

(Dragees)

Mol Wt 312 41

$C_{21}H_{28}O_2$

Δ^4-17-isopregnen—20-in —17β-ol—3-one

(17α—ethinyltestosterone or 20, 21-anhydro—17β—oxyprogesterone)

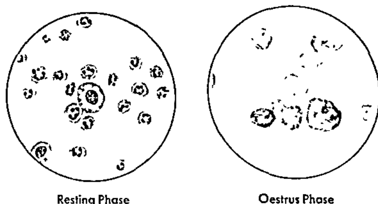
White crystals, stable in air Insoluble in water Soluble with great difficulty in the usual organic solvents Readily soluble in pyridine

F Pt = 266° C —267° C

$[\alpha]^{20}_{D}$ = + 21° C (Dioxane)

Fig 11

Fig. 9). Progesterone is changed biologically in the body to pregnandiol, a substance present in particularly large amounts in pregnancy urine (see Fig. 10). Pregnandiol is found in the urine during the secretory phase as well as after injection of pregnandiol, so that it is now regarded as the inactive excretory form of progesterone. The inactivation of orally administered hormones by passage through the liver has already been men-



Resting Phase   Oestrus Phase

Fig 12 Vaginal smears from rodents in the Allen-Doisy test

tioned, as with ethinyloestradiol, this leads to the development of pregneninolone (see Fig 11). This has an ethinyl group in the 17 position on the 5-carbon ring, and is equally active by mouth and progestationally.

Biological and chemical methods are used for the quantitative evaluation and the testing of the biological effect of oestrogen. The most commonly employed biological test, the Allen-Doisy test, depends on the demonstration of non-nucleated, keratinized epithelial cells in the vaginal smear of castrated female mice or rats [36] due to the desquamative phase appearing after the injection of oestrogen (see Fig. 12).

The non-esterified hormone preparations are standardized in international units (i. u.) and the benzoate esters in international benzoate units (i. b. u.). One i. u. represents the oestrus-producing effect of 0.1 gamma oestrone, and one i. b. u. that of 0.1 gamma oestradiol monobenzoate (one gamma = 0.001 mg.). The term rat or mouse unit (r. u. or m. u.) is used for the smallest amount of a substance required to induce oestrus in 50% of experimental animals. In Germany, 1 m. u. equals 5 i. u.

In addition to biological methods chemical test techniques are also used; these often involve colorimetric determinations [37, 38, 39].

The same principles govern the determination of the effect of corpus luteum hormone. The biological test [40, 41] is carried out on castrated rabbits, or better still on infantile ones. The yardstick is the transformation of the endometrium from the proliferative to the secretory phase induced by progesterone.

One i. u. corresponds to the effect of 1 mg. progesterone. The intramuscular dose of 5 mg. progesterone on 5 occasions, necessary for the development of the secretory phase, is equal to 100 clinical units. Hence 1 mg. progesterone corresponds to 4 clinical units or 2 rabbit units or 1 i. u.

The quantitative determination of oestrogen in the urine is of clinical significance in the case of menopausal women suspected of having adrenal cortical or ovarian tumours with endocrine activity. A relatively high excretion of oestrogen in the urine is also observed in men with adrenal carcinoma. The diagnostic value of the excretion of progesterone as pregnandiol depends in the first place on the demonstration of a disturbance of pregnancy [42].

Follicular hormone taken by mouth and swallowed is absorbed by the gastro-intestinal tract, but the hormone is to a large extent inactivated by passage through the liver [737].

This inactivation by the liver can be avoided by b u c c a l administration (placing the tablets in the canine fossa between the upper jaw and the upper lip). In this way the active agent is absorbed through the buccal mucosa and passes directly into the venous circulation (cf. page 107). On the other hand, ethinyl oestradiol is fully effective b y m o u t h [331, 335]. Alcoholic solutions are readily absorbed without great loss p e r l i n g u a l l y, i. e. also by short-circuiting the liver. Absorption from delicate skin areas (e. g. in the bend of the elbow or on the inner side of the thigh) is almost as good. Aqueous solutions are absorbed more rapidly parenterally than are oily ones (see pages 103 and 109). Increasing the dose does not cause more rapid onset of effect but simply prolongs the duration of action [13]. After i m p l a n t a t i o n of a tablet there is a slow and even flow of hormone into the body [44]. Increasing the dose however does not help the effect, but is more likely to cause "overflow," i. e. increased excretion [45, 46]. The speed and the amount of absorption of a tablet vary greatly with the individual patient, and depend upon the site of implantation, and the consistency and stereometric relationships of the tablet (cf. page 110).

On parenteral administration of progesterone, absorption is rapid and complete. The demonstration that when progesterone is administered by mouth (enterally) there is widespread inactivation by the liver led to the development of the orally active pregneninolone. As regards implantation, the remarks made about oestradiol tablets apply with equal force to progesterone tablets.

The various e f f e c t s o f o e s t r o g e n may be classified into genital and extragenital; both fields of action are of equal significance therapeutically.

The follicular hormone (oestrogen) is a growth hormone; hence the essential effect of the hormone is to cause proliferation and influence the growth of tissues (uterus, vagina, tubes, breasts). The uterus responds to administration of follicular hormone by

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oxycorticosterone) show the same or similar effects, though not *in the same dosage* [65, 66].

Corpus luteum hormone particularly affects the uterus. The pro-



Histological picture of the vaginal mucosa of a castrated woman before oestrogen treatment



The same mucosa after oestrogen treatment

Fig. 13

liferated and therefore functioning endometrium is transformed by its influence into the secretory phase, and hence prepared for the implantation of the ovum. If conception does not take place,

true growth, with mucosal proliferation and increase in weight [47]. The vaginal mucosa is stimulated to grow (Fig. 13), glycogen formation in its epithelium is promoted, and the occasionally neutral reaction of the vaginal secretion is restored to the physiological acid value (pH 4.5) [48]. The fallopian tubes react with hyperaemia, growth, mucosal proliferation and an increase in motility of the ciliary epithelium, which assists the transport of the ovum to the uterus by the tubes [49, 50]. The breasts show proliferation of the duct system [45]; oestrogen also prevents secretion of the lactation hormone through its inhibiting effect on the pituitary, and thus inhibits existing lactation. In animal experiments, follicular hormone may also lead, through stimulation of follicle growth, *to an increase in weight of the entire ovary, to promotion* of maturation of the follicle and its *rupture*, and by an *effect* on the anterior pituitary to corpus luteum formation. Apart from the obvious growth manifestations, follicular hormone has an inhibiting influence on pituitary activity. It also sensitizes the uterus to the anterior pituitary hormone oxytocin [51], and aids the growth of the prostate and seminal vesicles, as is clearly demonstrable in animal experiments [52, 53, 54].

The extragenital effects of follicular hormone are characterized by a general hyperaemic action, with dilatation of vessels, especially those of the abdominal organs and the genitalia, as well as the cerebral and coronary vessels [55, 56, 57], by a favourable influence on the growth of hair [58], the motor function of the gall-bladder [59], the relaxation of spasm of smooth musculature [60], the blood picture [61], and the metabolism [62, 63, 64], by an increase *in mental* capacity and also by the cure of certain psychic disorders [25, 26], and by other actions.

The m o d e o f a c t i o n o f c o r p u s l u t e u m h o r m o n e is of a generative character. It was formerly the fashion to regard the *action* of this hormone as strictly specific, but this is no longer believed, since other steroid hormones (testosterone, des-

the corpus luteum regresses, hormone production ceases, and the endometrium is cast off, with the appearance of menstruation. Contractility of the uterine musculature is lowered [67], and the mucosa of the tubes is so changed that it is able to envelop the ovum during its transit with a protective layer of secretion, which is perhaps of significance for the nutrition of the ovum during its travels [68, 69, 70]. The effect on the ovary is shown by the inhibition of ovulation [71, 72, 73, 74]; it is mediated by the pituitary. This effect is of no practical significance since progesterone is first formed after ovulation has taken place. In very large doses, such as are not used in therapy, progesterone led to intrauterine death of the foetus in experiments on guinea-pigs [75].

Because it stimulates new formation of secreting glandular tissue in the breast, progesterone has an influence on lactation [66, 76].

Little is as yet known about the extragenital effects of progesterone. In animal experiments, water excretion was promoted by administration of progesterone [77]. Because progesterone weakens the mydriatic effect of atropine, a parasympathetic action has been assumed [78, 79, 80, 81]. It may be that this effect is the reason for the clinical successes of progesterone therapy in glaucoma [82, 760]. *Corpus luteum hormone has recently been said to have* a favourable influence on carcinoma [738, 739, 740].

The physiological effects of the different female sex hormones are mutually balanced throughout the entire duration of life. Excessive or deficient supply of hormones leads to pathological disturbances. The following is the picture of conditions during the various phases of life (see also Fig. 14).

Even the embryo is under the influence of oestrogen. Because of the high level of oestrogen present in the embryo during the last weeks of foetal life, the foetal uterus in the female enlarges. For this reason also, vaginal bleeding may be observed in female infants at about the 5th to 6th day after birth as a withdrawal phenomenon, and the secretion of "witches' milk" from the

breasts of both boys and girls is common. Apart from withdrawal bleeding due to the sudden fall in oestrogen level, glycogen disappears from the vaginal epithelium, and this in its turn makes the infantile vagina more sensitive to infections.

The development of follicles in the ovaries of girls during childhood probably depends on the fact that the central nervous system slowly matures, and the follicle-stimulating hormone of the anterior pituitary then acts upon the infantile ovary. These follicles are never more than a half centimetre in diameter and subsequently disintegrate. With the onset of puberty (in Europe mostly between the 13th and 14th years) the follicular and corpus luteum hormones become of importance for the development of the female organism. During the period of physical and mental development of the girl, the effects of these hormones determine to a large extent the typical feminine character of the individual. In conjunction with other endocrine glands, they bring about the completion of growth, influence the vegetative functions of the central nervous system, and cause the appearance of the secondary sex characters (breasts, hair growth, voice, etc.).

With the beginning of sexual maturity, a follicle grows to a diameter of more than half a centimetre, ruptures after about 14 days of growth, and extrudes an ovum. This first ovulation is the real beginning of sexual maturity The ruptured follicle is transformed into the corpus luteum, and the latter begins to secrete corpus luteum hormone. If the ovum is not fertilized, the first menstrual period occurs by extrusion of the uterine mucosa, now in the secretory phase. In this way the menstrual cycle begins, and now continues physiologically over regular intervals of 21 to 30 days with an average of 28 days. However the first menstrual periods, like those in the so-called preclimacteric, often represent anovular bleeding in which no ovum is cast off from the follicle.

The secretion of ovarian hormones is in the main regulated by the anterior pituitary (see page 81) The follicle-stimulating hor-



mone of the anterior pituitary promotes the growth of the follicle but does not lead to its rupture. The latter occurs only under the influence of small supplementary amounts of luteinizing hormone, which complete the maturation of the follicle, and also bring about luteinization of the theca cells. If the oestrogen level has reached a certain point, the secretion of follicle-stimulating hormone is to a great extent inhibited by the oestrogen, the luteinizing hormone of the anterior pituitary comes into action and causes progesterone formation by the corpus luteum.

Changes in the uterine mucosa are regulated by the ovarian hormones, and run parallel to the secretion of the latter (see Figs. 15 and 16).

Follicular hormone causes cell proliferation in the tunica propria and the glandular epithelium, and thus a true endometrial growth (proliferative phase). After ovulation, the corpus luteum hormone leads to increased secretion from the glands of the endometrium, to increase in blood supply to the interstitial tissue, and to development of the so-called spiral vessels. Because of these changes, the mucosa enters into the stage of secretion. If fertilization does not occur, the mucosa is cast off in the form of menstruation, the corpus luteum of the ovary perishes, and the cycle begins again. If however fertilization and implantation of the ovum have occurred, the corpus luteum develops further to form a corpus luteum of pregnancy, which continues the secretion of progesterone and is at first responsible for the retention of the mucosa and thus for pregnancy continuation.

These physiological processes were the starting point for imitation of the natural cycle in the castrate, and also for the demonstration of the doses necessary for substitution therapy [83]. Since rupture of the follicle usually takes place between the 12th and the 16th days after menstruation, 5 mg. of oestradiol benzoate was given intramuscularly 5 times during the first 20 days, and 5 mg. daily of progesterone on each day from the 21st to the 25th days (reconstructive dose for castrates).

After this course, a true menstrual period appeared on the 2nd to 4th day after the last progesterone injection. By serial curettage during the course of this artificially created cycle it was possible to demonstrate the specific effects of follicular and corpus luteum hormone, and *to show histologically the changes described as typical in the endometrium of a castrate. Since the quantities of hormones necessary to produce the normal* cyclical changes in the endometrium of a castrate vary with the nature of the preparations employed, a review is given on page 103 of the differences in effects of the latter.

It has *already been stated* that if *pregnancy* occurs the corpus luteum continues to form progesterone. The embryonic trophoblast forms gonadotropic hormone, chorionic gonadotropin, which further prevents the premature disappearance of the corpus luteum of *pregnancy* (see Fig. 17). Hence the *endometrium is transformed* into the decidua of pregnancy under the influence of corpus luteum hormone. With participation of the chorion, the decidua forms the placenta, which now not only serves for embryonic nutrition but also functions as a gland of internal secretion. Because the production of chorionic gonadotropin slowly diminishes, *the corpus luteum of pregnancy degenerates, usually from about* the 4th month on. The placenta now takes over alone the production of the necessary amounts of luteal and follicular hormone (Fig. 18) The chorionic gonadotropin which it also produces abundantly apparently replaces the function of the anterior pituitary. In any case, it has been shown that during pregnancy the latter does not give rise to any notable amount of gonadotropic hormone [732].

Because luteal hormone exercises an inhibitory effect on motor excitability of the uterine musculature, it directly favours the growth of the embryo. The oxytocic effect of the posterior pituitary hormone *oxytocin is inhibited for the duration of* pregnancy. Later in pregnancy, the follicular and luteal *hormones* lead to the growth of the breasts and prepare them for lactation

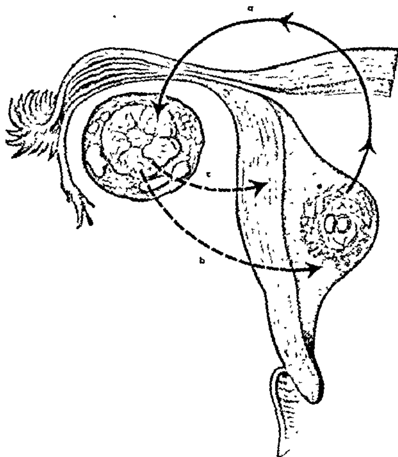


Fig 17. The action of chorionic gonadotropin in prolonging corpus luteum function, and its consequences

a) Chorionic gonadotropin maintains the function of the corpus luteum. Because of this,

b) the corpus luteum ensures the further maintenance and development of the decidua of pregnancy, and

c) the corpus luteum keeps the *uterine musculature at rest*

[79, 84, 74]. The maturation of growing follicles is prevented by inhibition of the follicle-stimulating factor of the anterior pituitary.

The different hormone levels present during pregnancy are shown in Fig. 19. The high oestrogen level at the end of pregnancy leads, in conjunction with factors as yet unknown, to sensitization of the uterus for the oxytocin of the posterior pituitary, and is in part held responsible for the onset of labour. Labour and the subsequent expulsion of the placenta lead to a sudden fall in the level of oestrogen. In consequence, the inhibiting influence of oestrogen on the anterior pituitary is removed. The latter now secretes the lactation hormone, prolactin, which brings on the secretion of milk. Under the influence of the folliculotropic factor of gonadotropic hormone a follicle ripe for rupture develops in the ovary. This follicle will however develop into the so-called corpus luteum of lactation, which degenerates only after lactation has completely ceased [79]. Thereafter the first true "cyclical follicle" matures, and the normal cyclical rhythm is resumed.

The cessation of the period of reproduction is characterized by disturbances in the genital sphere and in general health. The epoch of this physiological process, or the period of gradual extinction of sexual function (usually in the fifth decade of life in the woman), is designated the climacteric (see page 148). A sometimes brief but often prolonged stage of hyperendocrinism (hyperfolliculinism or hyperoestrinism — cf. page 54) is followed by a recession of oestrogen formation, which leads to the cessation of the cycle and finally to the menopause. The release of pituitary function causes an increase in tropin secretion The spreading reshuffle of hormones affects a number of other endocrine organs, so that signs of deficiency and of hyperfunction appear. These individually variable endocrine processes not infrequently lead to pathological manifestations requiring treatment

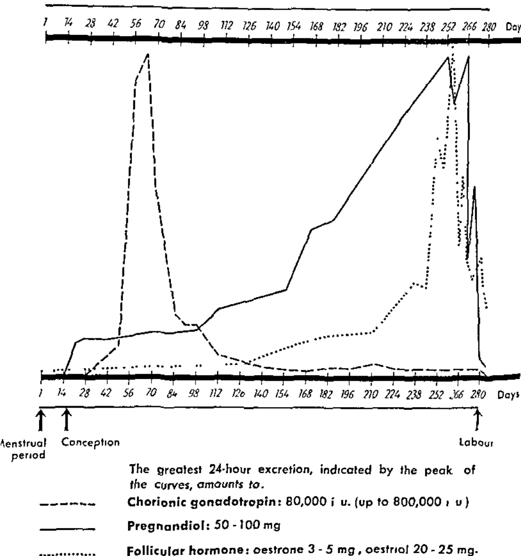


Fig 19 The excretion of chorionic gonadotropin, pregnandiol, and follicular hormone (oestrone plus oestriol) in the urine during pregnancy.

(After Hohlweg)

The changes in endocrine processes at the age of involution and in old age may cause disease of the vagina, whose physiology is greatly under the influence of endocrines. Under physiological endocrine conditions oestrogen causes deposition of glycogen in the vaginal epithelium. Döderlein's bacilli thus find a suitable nutrient medium, form lactic acid and thus create an acid medium (pH 4.5), which in its turn is a prerequisite for the biological cleansing of the vagina. If these processes are disturbed, the clinical pictures described on pages 142/143 occur. The vaginal epithelium responds to oestrogen and also to progesterone. In fact the vaginal epithelium responds to doses of oestrogen which are too small to affect the endometrial glands [85]. The demonstration of an oestrogen effect on the vaginal epithelium [86] does not signify that the endometrium has reacted in a similar manner. Study of the vaginal epithelium is one of the most sensitive methods of detecting the effect of the hormone

Over a long period the endocrine changes occurring at the menopause lead to a physiological atrophy of the internal sex organs (uterus, ovaries, tubes), but not always to extinction of libido or alteration in sexual behaviour. The psychical changes characteristic of the elderly (depression, lability of mood, etc.) may often be regarded as signs of hormone deficiency.

Follicular hormone has a series of extragenital effects, which are now utilized in therapy. The most outstanding is its influence on blood supply and distribution in certain areas (abdominal, cerebral, skin and cardiac vessels). Dilatation of the vessels is probably the result of the liberation of acetylcholine [57]. Because of an effect on the bone marrow, frequent administration of oestrogen causes increase in erythrocytes and haemoglobin [57]; metabolism is also favourably influenced [87, 88].

Female sex hormones also have an effect on the male organism. These heterologous effects are quantitative, and are related to the age of the patient and the chemical nature of the substance administered Oestrogen exercises its most marked effect on the

growth of the prostate, vas deferens and seminal vesicle, and breast [89]. Administration of oestrogen is followed by hypertrophy of the smooth muscle and the connective tissue, and the epithelia of the ducts of these glands proliferate. The cause of the prostatic hypertrophy is considered by many authors to be a disturbance of balance between the male hormone and the female oestrogen. The preponderance of oestrogen over the male hormone which must accompany involution leads to growth of the glandular component of the prostate (adenoma) [90, 91]; cf. page 172. In spite of this, oestrogen appears to lead to improvement in micturition in certain cases of hypertrophy. It has been shown that with high doses of oestrogen atrophy of the external glands may be obtained [92]. The male breast also responds to administration of oestrogen by growth of glandular epithelium [78, 93] (see page 174). Large doses of the follicular hormone also lead to marked feminization of the entire body [79].

The effects of progesterone so far described in the case of the male are of no significant therapeutic interest; they are to some extent controversial or insufficiently confirmed [21, 22, 94, 95].

It is also known that the two female sex hormones act synergistically in certain proportions. Corpus luteum hormone can change the endometrium into the secretory stage only when oestrogen is present. In physiological conditions the female organism also contains male sex hormones, whose significance will be discussed in the next chapter.

The physiological and pharmacological facts described above have led to formulation of certain treatment principles, set out on pages 220 et seq

Chemistry, Physiology and Pharmacology of the Male Sex Hormones

Male sex hormones are formed in the testis. The majority of investigators consider that the site of formation is the interstitial cells of Leydig, while others believe that the germinal cells or the cells of Sertoli are responsible. It has recently been shown that the adrenal cortex also produces androgens. In fact, this source of male sex hormones is quite considerable. In castrates two-thirds of the normal quantity of sex hormones may be found and this must have come from the adrenal cortex. It has also been established that the female adrenal cortex forms male sex hormone in exactly the same amounts as the male. Hence the male sex hormone is not "sex-specific" as used to be assumed but has quite specific functions in both sexes (96, 97, 98, 99) (cf. page 159).

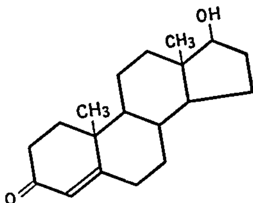
Androsterone, the form of male sex hormone excreted in the urine of men (100) (cf. Fig. 20), was first obtained as a pure crystalline substance in 1931 (101). In contrast to oestrogens, the aromatic six-carbon ring is missing from its constitutional formula. A keto group and a hydroxyl group are however present A few years later, the chemically pure hormone testosterone (see Fig. 21) was successfully isolated (102) and the substance synthesized from cholesterol (9, 103) As in the case of oestrogens, this gave the impetus to therapeutic employment of the hormone on a large scale It very soon became possible to increase the efficacy of the hormone by esterification with propionic acid (Testoviron in oily solution is testosterone propionate; cf. Fig. 22). The introduction of a methyl group into the 17 position in the five-

growth of the prostate, vas deferens and seminal vesicle, and breast [89]. Administration of oestrogen is followed by hypertrophy of the smooth muscle and the connective tissue, and the epithelia of the ducts of *these glands proliferate. The cause of* the prostatic hypertrophy is considered by many authors to be a disturbance of balance between the male hormone and the female oestrogen. The preponderance of oestrogen over the male hormone which must accompany involution leads to growth of the glandular component of the prostate (adenoma) [90, 91]; *cf.* page 172. In spite of this, oestrogen appears to lead to improvement in micturition in certain cases of hypertrophy. It has been shown that with high doses of oestrogen atrophy of the external glands may be obtained [92]. The male breast also responds to administration of oestrogen by growth of glandular epithelium [78, 93] (see page 174). Large doses of the follicular hormone also lead to marked feminization of the entire body [79].

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TESTOSTERONE

TESTOVIRON

(Implants and alcoholic solution)

The form of male sex hormone active in the organism   Mol Wt 288 41

$C_{19}H_{28}O_2$

Δ^4-androstene—17 β-ol—3-one

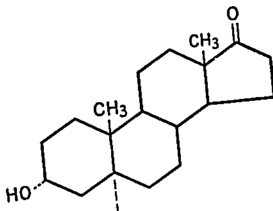
White, odourless crystals, stable in air Sparingly soluble in water Soluble in alcohol, ether and other organic solvents Slightly soluble in plant oils Of slight stability in presence of weak acids, alkalis, heat and digestive enzymes. Esterification with acids leads to increase of effect and prolongation of duration of action

F Pt = 154 5° C —155 5° C (corrected)

$[\alpha]_D^{20} = +109°$ C (in alcohol)

Occurrence in the testis

Fig 21



ANDROSTERONE

(Urine-excretory form) Mol Wt 290 13

$C_{19}H_{30}O_2$

Androstane—3α-ol—17-one

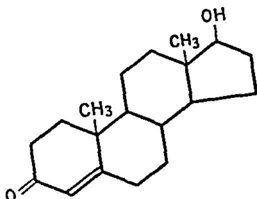
White, odourless crystals, stable in air Almost insoluble in water Soluble in dioxane, alcohol, chloroform and acetone Soluble with difficulty in plant oils

F Pt = 183 5° C —184 5° C (corrected)

$[\alpha]_D^{20} = +94°$ C (in alcohol)

Occurrence In the urine of males and females (also during pregnancy and after castration), bulls, and cows in calf

Fig 20



TESTOSTERONE

TESTOVIRON

(Implants and alcoholic solution)

The form of male sex hormone active in the organism — Mol Wt 288 41

$C_{19}H_{28}O_2$

Δ^4-androstene—17 β-ol—3-one

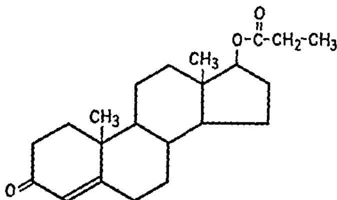
White, odourless crystals, stable in air Sparingly soluble in water Soluble in alcohol, ether and other organic solvents Slightly soluble in plant oils Of slight stability in presence of weak acids, alkalis, heat and digestive enzymes Esterification with acids leads to *increase* of effect and prolongation of duration of action

F Pt = 154 5° C —155 5° C (corrected)

$[\alpha]_D^{20} = +109°$ C. (in alcohol)

Occurrence in the testis

Fig 21



TESTOSTERONE PROPIONATE

TESTOVIRON

(Oily solution in ampoules)

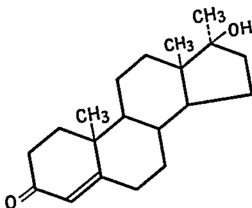
$C_{22}H_{32}O_3$ Mol Wt 344 48

Testosterone—17-propionate

White, odourless crystals, stable in air Insoluble in water Very soluble in alcohol, ether and other organic solvents Relatively easily soluble in plant oils

F Pt = 121° C—122° C

$[\alpha]_D^{20}$ = + 84° C (dioxane)



METHYL TESTOSTERONE

TESTOVIRON

(Buccal tablets)

Mol Wt. 302 44

$C_{20}H_{30}O_2$

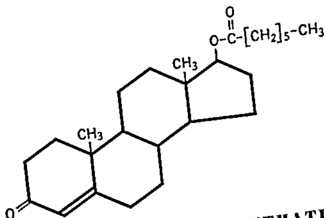
17α methyl—Δ^4-androstene—17β-ol—3-one

White, odourless crystals, stable in air Sensitive to light Insoluble in water. Soluble in alcohol, ether and other organic solvents Slightly soluble in vegetable oils

F. Pt = 165° C

$[\alpha]_D^{20}$ = + 83° C (in alcohol)

Fig 23



TESTOSTERONE OENANTHATE

Testoviron-Depot (ampoules)

Mol Wt 400 58

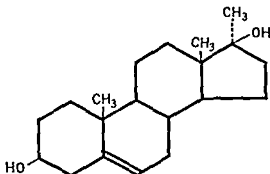
$C_{26}H_{40}O_3$

White crystalline powder, turning waxy at high room temperature, of very slightly rancid odour, non-hygroscopic Insoluble in water, readily soluble in all common solvents and also in vegetable oils

F Pt = 37° C — 38° C

$[\alpha]_D^{20} = + 78°$ C (dioxane)

Fig 21



METHYLANDROSTENEDIOL

(Ampoules)

$C_{20}H_{32}O_2$ — Mol Wt 304.46

17α-methyl—Δ⁵-androstene—3β, 17β-diol

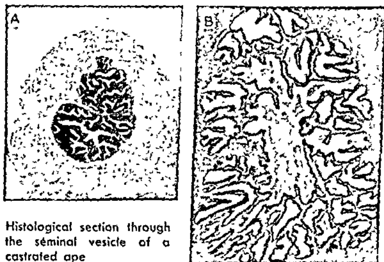
White, loose, odourless powder, insensitive to light, practically insoluble in water, readily soluble in alcohol, soluble with great difficulty in ether. Slightly soluble in vegetable oils

F. Pt = 205.5° C —206.5° C (corrected)

$[\alpha]_D$ = — 73° C (in alcohol)

Fig 25

after giving a loading dose of creatine more than 10% of creatine is excreted in 24 hours, this indicates testicular insufficiency. Values under 10% suggest other causes. However, lack of vitamin E also leads to creatinuria, and this has been observed in other conditions such as Graves's disease and Addison's disease



Histological section through the seminal vesicle of a castrated ape

(A) untreated, (B) treated with testosterone

Fig 28

[109, 110]. The situation is very complicated, and the value of the test is therefore controversial [111].

The clinical value of methods for the determination of androgens in the urine and blood is limited, since there is a wide range of physiological variation Age and sex contribute to the great variability. Only abnormally high values can therefore be taken into account [12]. In assessing these methods, it must be borne in mind that considerable amounts of androgen are excreted with the bile into the intestine and therefore lost to the urine.

The absorption of testosterone is basically governed by the same factors as that of female sex hormones.

As with female sex hormones, the *effects of male sex hormones* may be classified as genital and extragenital.

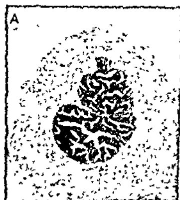
Sexuality (the characters and behaviour specific for the male) is determined to a great extent by the gonadal hormones. Processes taking place in the central nervous system are to some extent stimulated by gonadal hormones; on the other hand, the central nervous system has an effect on the formation of gonadal hormone. A male sexual cycle comparable to the female one is unknown. Nevertheless the man, the young male child and even the embryo are unter the influence of pituitary hormones, especially the gonadotropic hormones of the anterior lobe [9, 112], which lead to stimulation of the testes with increasing maturity of the central nervous system.

Normally, descent of the testes into the scrotum occurs before birth. However the testes do not always descend. Administration of gonadotropic hormones leads indirectly by liberation of gonadal hormones to descent [112, 113, 114, 115]. Descent ensures the normal development of the testes, and thus the further physiological development of the male organism. If descent does not take place, pressure and warmth in the lower abdomen or inguinal canal cause damage to the hormone-secreting cells of the testes and to the clinical conditions described on page 170.

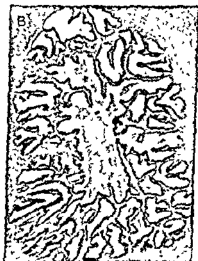
Preponderance of the substances which confer male characteristics begins slowly in boys at about the 6th or 7th year of life. Play behaviour and the mode of reaction take on more and more the characters typical of the male, and are gradually intensified. The simultaneous appearance of follicular hormone evokes the occasional manifestation of "intersexual behaviour," which may because of pathological changes in the gonads or even the adrenals lead to an alteration in sex amounting to a pathological and endocrine-conditioned intersex (see page 188).

4*

after giving a loading dose of creatine more than 10% of creatine is excreted in 24 hours, this indicates testicular *insufficiency*. Values under 10% suggest other causes. *However, lack of vitamin* E also leads to creatinuria, and this has been observed in other conditions such as Graves's disease and Addison's disease



Histological section through the seminal vesicle of a *castrated ape*



(A) *untreated*, (B) *treated with testosterone*

Fig. 28

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daily usually restores libido and potency after a short while. A daily dose of 5—10 mg. Testoviron intramuscularly is generally required for maintenance. The level of dosage depends on the preparation employed (see page 103).

In the interplay between testis and anterior pituitary, testosterone inhibits the activity of the latter in a manner similar to follicular hormone, but to a significantly lesser degree (see Fig. 51). In human subjects, however, only very high doses diminish the excretion of gonadotropic hormone [120]. If the pituitary is removed, the internal secretion of the testes ceases because the effect of gonadotropic hormone is absent (cf. page 81).

Among the extragenital effects of testosterone, its influence on the circulation and the psyche are the most prominent [121, 122, 123, 124, 125]. Administration of testosterone diminishes the tonus of and dilates the cerebral vessels, with restitution of the lipochrome ganglion cells [126]. Other authors have observed a rise in expiration pressure in emphysema in the elderly, and a restoration of diminished muscle power in ageing men [127]. This probably depends on a true retention of nitrogen in muscle, whose capacity is thus increased [128]. This is designated as a myotropic effect, and the inhibiting influence on protein metabolism as an anabolic effect [129]. Another metabolic effect has been demonstrated in that testosterone, like follicular hormone, favours the deposition of calcium and phosphorus in bone; this fact is of significance in the treatment of bone tumors and osteoporosis [130, 131]. Administration of testosterone also raises the tonus of the urinary bladder [127], and because of vasodilatation and improvement of circulation has a favourable effect in cases of coronary spasm, endangiitis obliterans and peripheral circulatory disturbance [121, 125, 132, 761]. The antidiabetic action of testosterone depends on the fact that it raises tolerance to carbohydrates [127, 133]. During the treatment of diabetes in the elderly there is a simultaneous improvement or disappearance of other manifestations of ageing due to endocrine factors. Cure of endo-

Normally, at puberty the secretion of male sex hormones becomes m o r e i n t e n s e. Because of this, growth is often temporarily arrested as a result of inhibition of the secretion of growth hormone by the anterior pituitary. The secondary sex characters (pubic hair, breaking of the voice, growth of genitalia, male physical conformation) appear. Concomitantly with these external changes, there is development of the type of behaviour characteristic of the male and differentiating him sharply from the female. The male becomes fertile (potentia generandi); libido and potency (potentia coeundi) appear and are preserved almost throughout the rest of life.

Hormonal processes are held responsible for the changes in capacity and mood which occur during maturity. These changes, together with a fall in capacity and in libido and potency, lead in conjunction with disturbances in endocrine correlation with other glands to generalized symptoms and signs, well known as the "male climacteric" [117]. The depression and the diminution in mental capacity which often appear at this epoch can be avoided by giving male sex hormone [25, 26]; this substance also cures disturbances of potency of endocrine origin.

With increasing age, a physiological atrophy of the sex organs may also occur in the male, though this is never so strongly marked as in the woman; psychical changes are, however, prominent. The intensity of these changes varies very greatly with the individual. The main g e n i t a l effect of male sex hormone is promotion of growth of the male sex organs. The penis, vas deferens, seminal vesicles, Cowper's glands and the preputial glands achieve full development. Clinical experience and extensive research have shown (particularly by implantation of testosterone into the testes) that testosterone exerts a direct growth-promoting effect on the testicular tissue [118, 119].

It is of clinical importance to determine the therapeutic doses necessary to remove the sequelae of castration in persons castrated late. Administration of 25 mg. Testoviron intramuscularly

daily usually restores libido and potency after a short while. A daily dose of 5—10 mg. Testoviron intramuscularly is generally required for maintenance. The level of dosage depends on the preparation employed (see page 103).

In the interplay between testis and anterior pituitary, testosterone inhibits the activity of the latter in a manner similar to follicular hormone, but to a significantly lesser degree (see Fig. 51). In human subjects, however, only very high doses diminish the excretion of gonadotropic hormone [120]. If the pituitary is removed, the internal secretion of the testes ceases because the effect of gonadotropic hormone is absent (cf. page 81).

Among the extragenital effects of testosterone, its influence on the circulation and the psyche are the most prominent [121, 122, 123, 124, 125]. Administration of testosterone diminishes the tonus of and dilates the cerebral vessels, with restitution of the lipochrome ganglion cells [126]. Other authors have observed a rise in expiration pressure in emphysema in the elderly, and a restoration of diminished muscle power in ageing men [127]. This probably depends on a true retention of nitrogen in muscle, whose capacity is thus increased [128]. This is designated as a myotropic effect, and the inhibiting influence on protein metabolism as an anabolic effect [129]. Another metabolic effect has been demonstrated in that testosterone, like follicular hormone, favours the deposition of calcium and phosphorus in bone; this fact is of significance in the treatment of bone tumors and osteoporosis [130, 131]. Administration of testosterone also raises the tonus of the urinary bladder [127], and because of vasodilatation and improvement of circulation has a favourable effect in cases of coronary spasm, endangiitis obliterans and peripheral circulatory disturbance [121, 125, 132, 761]. The antidiabetic action of testosterone depends on the fact that it raises tolerance to carbohydrates [127, 133]. During the treatment of diabetes in the elderly there is a simultaneous improvement or disappearance of other manifestations of ageing due to endocrine factors. Cure of endo-

crine-conditioned joint disorders [134 et al] and skin disorders [135, 136, 137 et al] has also been reported. The favourable influence of testosterone on mental efficiency and mood [25, 26, 138, 139] gives it a significant place in therapeutics. It has also been asserted that certain androgen compounds prevent degeneration of the renal parenchyma [140]; this so-called renotropic effect has so far not been used much in therapy [141, 142].

The heterologous employment of male sex hormone for women is now a commonplace. Ovarian function is inhibited via the pituitary; there is thus an indirect antagonism to follicular hormone. In correspondingly higher doses virilization occurs, with complete cessation of oestrous functions (endocrine castration) [143, 144, 145]. The therapeutic employment of androgens in women depends on these effects (see page 159). It is particularly indicated if too high a level of oestrogen has led to disequilibrium (hyperoestrinism). Treatment of breast carcinoma and genital carcinoma in women with testosterone continues to gain in importance (see pages 161 and 163) The highly concentrated Testoviron-Depot is especially suitable (see Fig. 24). Other androgens, such as methylandrostenediol (see Fig. 25) which does not lead to virilization, may be used in these cases [146]. Further work is necessary to clarify the question whether methylandrostenediol is equal or superior to testosterone as regards results [147, 148, 149].

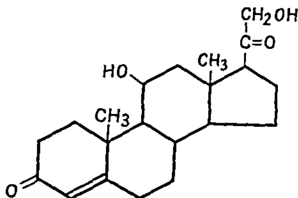
The therapeutic effect of fairly large doses of testosterone in metrorrhagias due to persistence of the follicle depends on a direct vasoconstrictor effect on the endometrial vessels [150] and on an indirect one via the anterior pituitary [151]. This indirect antagonistic action is also made use of in other gynaecological indications (see page 159). The principles of treatment which arise out of the considerations outlined above are described on pages 220 et seq.

Chemistry, Physiology and Pharmacology of the Adrenal Cortical Hormones

The adrenals consist of a cortex and a medulla Both segments, although morphologically and embryologically different, produce hormones. Adrenaline and l-noradrenaline arise from the medulla In the cortex, three groups of cortical hormone with different effects are formed: mineralocorticoids, glucocorticoids and the androgen steroids [152].

Chemical research on adrenal cortical hormones has made considerable progress in recent years [153, 154, 155, 156, 157]. A total of six substances have been prepared in pure crystalline form: corticosterone, desoxycorticosterone, 17-hydroxycorticosterone, 11-dehydrocorticosterone, 11-desoxy-17-hydroxycorticosterone and 11-dehydro-17-hydroxycorticosterone (see Figs. 29 to 34). These compounds are chemically related to progesterone. Desoxycorticosterone esterified with acetic acid (see Fig. 30) is more effective than the non-esterified hormone [158]. Preparation of the hormones from organs has proved uneconomic. After the steroid character of desoxycorticosterone had been elucidated, it was prepared by chemical synthesis from cholesterol [154]. Only after this synthesis was it possible to use the hormone extensively in therapy. One of the most important of these cortical hormones from a therapeutic standpoint is desoxycorticosterone, whose acetate is Primocort

For evaluation of desoxycorticosterone the "classical" test of its effect in prolonging life of adrenalectomized animals is used (life-maintenance test). Other authors use supplementary tests, in which they evaluate the behaviour of residual nitrogen or



CORTICOSTERONE

Compound B (Kendall)

Compound H (Reichstein)

$C_{21}H_{30}O_4$ Mol Wt 346 25

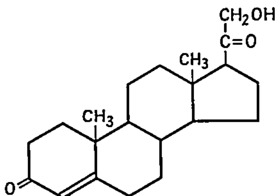
Δ^4-pregnene—11β, 21-diol—3,20-dione

Soluble in fat solvents and slightly in water

F. Pt = 180° C —182° C (corrected)

$[\alpha]^{15}_{D} = + 223° C \pm 3° C$ (alcohol)

Occurrence. adrenal cortex



DESOXYCORTICOSTERONE

Compound Q (Reichstein)

$C_{21}H_{30}O_3$ Mol Wt 330 22

Δ^4-pregnene—21-ol—3,20-dione

White, odourless crystals, stable in air Slightly soluble in water More readily soluble in alcohol, acetone, dioxane and vegetable oils

F Pt = 141° C—142° C

$[\alpha]_D^{20}$ = + 187° C (alcohol)

= + 173° C (dioxane)

Occurrence adrenal cortex

As acetate

PRIMOCORT (ampoules, tablets and implants)

$C_{23}H_{32}O_4$ Mol. Wt 372 49

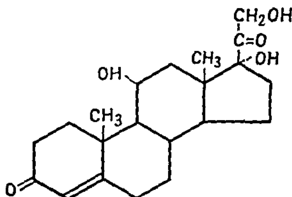
Δ^4-pregnene—21-ol—3,20-dione—21-acetate

White crystals, very slightly soluble in water, more readily soluble in alcohol, acetone, dioxane and vegetable oils

F. Pt = 157° C—158° C.

$[\alpha]_D$ = + 179° C ± 4° C (in chloroform)

Fig 30



17-HYDROXYCORTICOSTERONE

(Compound F Kendall)

Compound M (Reichstein)

$C_{21}H_{30}O_5$ Mol Wt 362 45

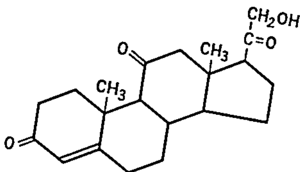
Δ^4-pregnene—11β, 17α, 21-triol—3,20-dione

Small crystals Recrystallizable out of acetone-acetate, out of water, out of isopropylalcohol

F Pt 216° C—221° C (corr) (decomp)

$[\alpha]_D^{24} = +163°$ C (methanol)

Occurrence adrenal cortex



11-DEHYDROCORTICOSTERONE

$C_{21}H_{28}O_4$ Compound A (Kendall)

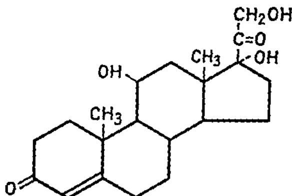
Δ^4-pregnene—21-ol—3, 11, 20-trione Mol Wt 344 43

F Pt. = 177° C —180° C

$[\alpha]_{546}$ = + 299° C

Occurrence adrenal cortex

Fig 32



17-HYDROXYCORTICOSTERONE

(Compound F Kendall)

Compound M (Reichstein)

$C_{21}H_{30}O_5$ — *Mol Wt* 362.45

Δ^4-pregnene—11β, 17α 21-triol—3,20-dione

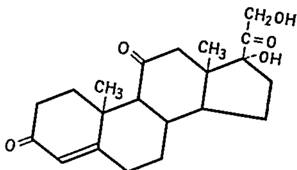
Small crystals Recrystallizable out of acetone-acetate, out of water, out of isopropylalcohol

F Pt. 216° C—221° C (corr) (decomp)

$[\alpha]_D^{21}$ = + 163° C (methanol)

Occurrence adrenal cortex

Fig 31



11-DEHYDRO-17-HYDROXYCORTICOSTERONE

Compound E (Kendall)
Compound Fa (Reichstein)
Compound F (Wintersteiner)
Cortisone

$C_{21}H_{28}O_5$ Mol Wt 360 44

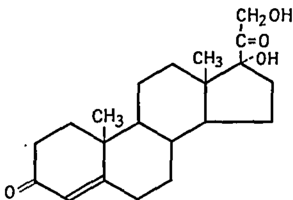
Δ^4-pregnene—17α, 21-diol—3,11,20-trione

F Pt = 215° C (corr) (decomp)

$[\alpha]_D$ = + 209° C (alcohol 95%)

Occurrence adrenal cortex

Fig 34



11-DESOXY-17-HYDROXYCORTICOSTERONE

Compound S (Reichstein)

$C_{21}H_{30}O_4$ Mol Wt 346 45

Δ^4-pregnene—17α, 21-diol—3,20-dione

F Pt = 207° C.—209 C.

Occurrence adrenal cortex

Fig 33

20 mg. per day (average 11 mg.), and is about one-third less in the female (average 7 mg.) [166]. In children, the figure is even smaller [167]. Values vary with the individual and also with age. The more the functional capacity of the adrenal cortex diminishes, the lower the 17-ketosteroid excretion in the urine [168, 169, 170]. On the other hand, it is raised in cases of adrenal cortical tumour and testicular tumour, in virilism and in pseudohermaphroditism. The determination of 17-ketosteroids is also of differential diagnostic significance, e. g. in Cushing's syndrome. If Cushing's syndrome is due to an adrenal cortical tumour the 17-ketosteroid excretion is extraordinarily high; in contrast, values are normal in pituitary Cushing's syndrome [171, 172].

As a technique of demonstrating differential secretion in the adrenal cortex, determination of corticoids in the urine can now be carried out with separation of mineralocorticoid and glucocorticoid excretion [173, 174, 741].

All these functional tests involve so difficult a technique that they can be carried out only in large clinics with well-equipped laboratories and trained personnel. The Robinson-Power-Kepler test seems suitable for the average clinical laboratory.

On o r a l administration (swallowing) even desoxycorticosterone acetate loses much of its activity by inactivation in the liver (cf. page 107) With p e r l i n g u a l administration, a proportion of the hormone is swallowed with the saliva and thus also rendered inactive On the other hand, b u c c a l employment (placing a tablet in the canine fossa between the upper lip and the jaw) ensures extraordinarily good absorption (cf. page 107), and almost complete utilization of the dose administered, with short-circuiting of the portal circulation. The hormone is either not stored in the organism or else stored in very small amounts [175]. The adrenal cortical hormone desoxycorticosterone has its chief influence on carbohydrate, fat and lipoid metabolism, on water and mineral balance and on enzyme metabolism [176, 177, 178 179, 757]. These effects are summarized in the tables on pages 64 and 65

urea, the increase in muscle performance (muscle-fatigue test) or the survival *time of guinea-pigs given diphtheria toxin* [159, 160, 161]. A rat unit is that quantity of hormone which must be given daily in two doses to adrenalectomized rats aged four weeks in *order to keep 50%* of the animals *alive* for at least *3* weeks. One rat unit (r. u) in the survival test corresponds to 0.3 to 0.6 mg. desoxycorticosterone.

Numerous methods have been suggested for testing adrenal cortical function. The most important of these are the Robinson-Power-Kepler test and the determination of 17-*ketosteroids* and corticoids in the urine.

The Kepler test depends upon the evaluation of disturbances of mineral and water economy which appear in adrenal cortical hypofunction. The usual water tolerance test is first carried out, and then the values for urea and chloride in serum and urine are related by use of a formula to the amount of urine excreted [162, 163, 161].

Determination of the 17-ketosteroids involves the excretory forms of the steroid hormones, which carry a keto group (CO) in the 17 or also the 20 position of the steroid skeleton and whose hydroxyl group on the C 3 atom has a neutral reaction [165, 107, 106]. They include the 17-hydroxycorticoids (e. g. cortisone and compound F) and the androgens from the adrenal cortex and the gonads. Demonstration of 17-ketosteroids is therefore a group reaction, by means of which a total of 40 ketosteroid compounds are determined These can be divided into an alpha and a beta fraction The alpha fraction contains the hormones from the gonads (e. g. androsterone), while the beta fraction mainly consists of hormones from the adrenal cortex [166]

Of the hormones involved in total ketosteroid determinations and their *degradation products,* about two-thirds come from the adrenal cortex and one-third from the gonads. The normal value for 17-ketosteroid *excretion* in the male lies between 10 and

3. Regulation of the Circulation:

by participation in·

a) regulation of blood volume and blood pressure b) increase in heart minute volume c) maintenance of capillary tonus	Counteraction of circulatory deviations in physical and psychical stress

In adrenocortical hypofunction hypotension, diminished capacity of the circulation for adaptation to stress (relationships to vegetative dystonia and to shock)

In adrenocortical hyperfunction hypertension, capillary changes (nephrotic syndrome, retinal changes)

4. Regulation of the Defence Functions of the Body:

a) Increase in resistance to toxins

b) Intervention in detoxication processes in the body (especially histamine detoxication)

c) Increase in phagocytic capacity of neutrophil leucocytes

In adrenocortical hypofunction increased sensitivity to infections and intoxications

5. Regulation of Growth:

(only in association with the diencephalo-pituitary system)

After adrenocortical extirpation cessation of growth, dwarfism in young animals

6. Influence on Heat Regulation:

In adrenocortical dysfunction disturbances of physiological capacity for heat regulation

7. Influence on Sexual Functions:

The adrenal cortex produces the raw materials for androgens and oestrogens The adrenal cortex also itself produces male and female sex hormones ("accessory sexual glands").

In adrenocortical dysfunction "Hormonal sterilization", hypogenitalism, interrenalism, virilism, gynaecomastia

8. Effects on the Interrelationships between Psyche and Metabolism:

Influence on the central nervous system
(limited euphorizing and narcotic action)

Functions of the Adrenal Cortical Hormone Desoxycorticosterone

1. Regulation of Total Metabolism:

The adrenal cortical hormone (A C hormone) desoxycorticosterone is the catalyst for all phosphorylation processes (esterification of glucose with phosphate).

It is necessary for:

a) glycogen formation from carbohydrate, or glycogenesis b) glycogen formation from protein and fat, or neoglucogenesis c) regulation of selective sugar absorption from the intestinal mucosa d) reabsorption of sugar in the renal tubules	*Glycogen deposition in liver and musculature* *Regulation of energy exchange in muscle*
e) promotion of intestinal absorption of fat and protein f) regulation of fat distribution by promotion of mobilization of fat in the tissues and fixation of tissue cholesterol	Prerequisites for the undisturbed sequence of fat and lipoid metabolism

Disturbances lead to *extrainsular glycosuria, ketonaemia, hypercholesterolaemia, and hyperlipoidaemia (relation to arteriosclerosis)*

2. Regulation of Water and Mineral Balance:

a) Displacement of intracellular fluid into the extracellular spaces and into the blood vessels b) Maintenance of electrolyte balance by mobilization of intracellular sodium and chloride, and fixation of potassium in the cell	Regulation of osmotic relationships Maintenance of the physiological Na/K quotient As a result, influence on the tonus of the autonomic nervous system.

In adrenocortical hypofunction depletion of NaCl, dehydration and rise in residual nitrogen.

In adrenocortical hyperfunction retention of NaCl and water

attempt of the organism to increase non-specific resistance to the damaging influence of any strain above the average. If the attempt fails, either as a result of too great or too prolonged a stress effect or in consequence of inherent incapability of the body, and the stress is not overcome, the regulating processes occurring during the AS are intensified to a pathological degree, and signs of illness appear as the so-called adaptation diseases. Basically, the AS always passes in the same manner through three phases. The latter are sharply defined by reason of the different regulation mechanisms appearing during the three.

The three phases are:

1. the alarm reaction;
2. the stage of resistance, or adaptation proper;
3. the stage of exhaustion.

Since every stressful stimulus, apart from its non-specific stress component, exercises certain specific effects simultaneously, depending on its nature (e. g on the affected tissues or on certain organ systems), the AS never appears in pure form. It is always complicated by supplementary specific reactions. This is the explanation for the polymorphism or protean nature of the symptoms in the AS. During the alarm reaction adrenocorticotropic hormone (ACTH) is secreted by the anterior pituitary in increased amount. Simultaneously, the formation and output of adrenaline and l-noradrenaline from the adrenal medulla are increased. There is hypertrophy of the adrenal cortex, with increased secretion, principally of glucocorticoids. Other changes include disappearance of lymphatic tissue (involution of the thymus and lymph nodes), changes in the reticulo-endothelial apparatus (increased phagocytosis and antibody formation), alterations in the blood picture and the composition of the blood proteins (eosinopenia, lymphopenia, neutrophil granulocytosis, shift to the left, fall in erythrocyte sedimentation rate), increased neoglucogenesis (new formation of carbohydrates out of protein and fat), gastro-intestinal erosions, and displacements in mineral

Certain research workers [176, 180] have for long supported the unitary (phosphorylation) theory of adrenal cortical hormones, and others a dualistic theory [153, 181]. According to the unitary theory, desoxycorticosterone is the omnipotent hormone, and the remaining adrenal cortical hormones are merely derived by degradation or synthesis from desoxycorticosterone. On this view, the physiological differences between the various hormones are to a large extent quantitative, conditioned by their greater or lesser solubility in water.

On the other hand, according to the dualistic theory mainly supported by American authors, there are two groups of adrenal cortical hormones: the mineralocorticoids with a primary effect on electrolyte and water economy, and the glucocorticoids chiefly influencing carbohydrate metabolism. According to this theory, desoxycorticosterone and compound S belong to the group of mineralocorticoids.

All so-called 11-hydroxycorticosteroids (the recently discovered cortisone or compound E, now prepared in pure form, corticosterone or compound B, compound A, and Kendall's compound F), however, belong to the group of glucocorticoids [153, 154, 155, 182] The most recent research suggests that the adrenal cortex and the pituitary are in the front rank of defence against injuries to the body of any nature [157, 183, 184, 185, 186].

According to the working hypothesis of these researchers, any stress on the organism may be of very diverse nature, and may be provoked by chemical agents, infections, physical or mental strain

The organism responds to any kind of stress constantly with the same type of reaction, whose systematic course is independent of the specific nature of the current stress. This basic biological reaction in response to any stimulus exceeding the normal is called the general adaptation syndrome (AS). The AS is necessary to life and represents an adaptation process in the body to special demands incurred through the action of stress. It is the

attempt of the organism to increase non-specific resistance to the damaging influence of any strain above the average. If the attempt fails, either as a result of too great or too prolonged a stress effect or in consequence of inherent incapability of the body, and the stress is not overcome, the regulating processes occurring during the AS are intensified to a pathological degree, and signs of illness appear as the so-called adaptation diseases. B a s i c a l l y , the AS always passes in the same manner through three phases. The latter are sharply defined by reason of the different regulation mechanisms appearing during the three.

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and water metabolism. All these changes represent active defence measures on the part of the organism against the damaging stimulus, and serve to adapt the organism to the changed conditions due to the stress. *This process of adaptation is attained in the* s t a g e o f r e s i s t a n c e. There now exists a special resistance to the factor causing the stress, but a simultaneous lowering of resistance to any other stress which may crop up. If the specific stress continues for too long, or a new and different type of noxious stimulus is added, the stage of resistance passes over into the s t a g e o f e x h a u s t i o n. In this phase of the AS *the body loses its capacity for adaptation. Resistance is paralysed*, and there is a complete breakdown of all purposeful regulation, with cachexia and death of the individual as consequences. If these reactions of the general adaptation syndrome take place in an excessive or abnormal manner, the various adaptation diseases *arise as results of metabolic disequilibria in the adaptation* mechanism of the stage of resistance, because of endocrine dysfunction (disturbance of balance between the required amounts of glucocorticoids and mineralocorticoids).

These new theories of American authors show the partial antagonism which exists in the dualistic view of things between glucocorticoids and mineralocorticoids. However, this sharp division between the two groups of adrenal cortical hormones does not seem to be justified in the light of the most recent results of research, since the various cortical steroids of the two groups frequently overlap as regards effects. Thus, for example, all the glucocorticoids so far studied have certain additional effects like mineralocorticoids on the metabolism of Na, Cl, K and water

According to these views, desoxycorticosterone is a mineralocorticoid, and influences mineral metabolism to a much greater extent than do the glucocorticoids. Only cortisone and the other 11-hydroxycorticosteroids cause the changes described above in the lymphatic tissue, the reticuloendothelial system and the blood picture.

Cortisone and desoxycorticosterone in large doses have the same type of action on the kidney. There is first a hypertrophy of the organ with proliferation of the perivascular connective tissue. Later the renal arterioles contract, and in consequence the kidney secretes a hypertensive substance renin, which causes high blood pressure and its sequelae cardiac hypertrophy, arteriosclerotic changes, and so on. The renal effect of desoxycorticosterone, which appears only as a sign of overdosage after prolonged administration of very large doses, can be arrested by omitting sodium chloride. Very excessive doses of glucocorticoids may lead to permeability of the glomeruli for protein and blood, and finally to hyalinization and sclerosis of the glomeruli, and thus to nephrosclerosis.

The rise in blood pressure which is caused by the hypertensive substance in the kidneys in the presence of sodium chloride, is said to be dependent on the presence of a pituitary factor "X". This factor X has been demonstrated so far only in crude extracts of pituitary and in the so-called "lyophilized" anterior pituitary tissue (very finely emulsified pituitary tissue in solution). It is certainly n o t identical with ACTH, but may be a mixture of other known pituitary hormones or possibly identical with the growth hormone. At any rate, factor X appears to be a specific principle of the anterior pituitary, since it is not present in other tissue extracts equally rich in protein.

If the diet is deficient in protein the factor is not formed This is the explanation of the favourable effect of a diet poor in salt and protein in nephrosclerosis. The deficiency of salt renders ineffective the onslaught of adrenal cortical hormones on the renal vessels. In spite of existing renal vascular changes, the lack of protein arrests the formation of hypertensive substance in the kidney, by deficient preparation of the factor X in the pituitary. These changes, which are not limited to the kidney but may lead to vascular damage in the rest of the body, appear to play a part in the stage of exhaustion after stress.

and water metabolism. All these changes represent active defence measures on the part of the organism against the damaging stimulus, and serve to adapt the organism to the changed conditions due to the stress. This process of adaptation is attained in the stage of resistance. There now exists a special resistance to the factor causing the stress, but a simultaneous lowering of resistance to any other stress which may crop up. If the specific stress continues for too long, or a new and different type of noxious stimulus is added, the stage of resistance passes over into the *stage of exhaustion. In this phase of the AS* the body loses its capacity for adaptation. Resistance is paralysed, and there is a complete breakdown of all purposeful regulation, with cachexia and death of the individual as consequences. If these reactions of the general adaptation syndrome take place in an excessive or abnormal manner, the various adaptation diseases arise as results of metabolic disequilibria in the adaptation mechanism of the stage of resistance, because of endocrine dysfunction (disturbance of balance between the required amounts of glucocorticoids and mineralocorticoids).

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According to these views, desoxycorticosterone is a mineralo-*corticoid*, and influences mineral metabolism to a much greater extent than do the glucocorticoids. Only cortisone and the *other* 11-hydroxycorticosteroids cause the changes described above in the lymphatic tissue, the reticuloendothelial *system and the* blood picture.

Addison's disease develops after destruction of the adrenals, e. g. by tuberculosis, or their complete removal. In this disease the glycogen content of muscles and liver is lowered while the lactic acid content of the musculature is raised. Blood pressure and body temperature are lowered The sodium and salt levels in the blood are lowered. The ratio of sodium to potassium is displaced in favour of potassium. Potassium is withdrawn from the tissue cells which consequently have a higher content of sodium and chloride; both elements are simultaneously excreted in greater amounts in the urine. These changes lead to concentration of the blood (with increase in viscosity), polyglobulia, increased strain on the circulation and cardiac insufficiency. The cholesterol and residual nitrogen content of the blood also increases, fat absorption is disturbed (fatty stools), and the blood sugar level falls. In association with this, there is a definite lowering of the resistance of the organism to infections and toxins.

These manifold, severe symptoms and signs of fully developed Addison's disease disappear on administration of desoxycorticosterone but not on administration of cortisone alone. They are the consequences of disturbance of regulation of metabolism of carbohydrates, fat and enzymes, as well as of water and mineral balance. Combination of carbohydrates with phosphoric acid is necessary for selective absorption of carbohydrate (glucose and galactose) from the intestine, for transformation of sugar into glycogen, and for changing the lactic acid arising through muscular activity into sugar and glycogen Fats are also only absorbed after addition of phosphoric acid. This process of intermediate phosphorylation can only continue undisturbed if sufficient desoxycorticosterone is present in the blood and tissues. The presence of this adrenal cortical hormone is also absolutely necessary for the smooth running of salt metabolism and water metabolism. There are also relationships between the adrenal cortex and the metabolism of vitamins and enzymes, e. g. in pellagra and sprue [177, 181, 193, 194, 195]. As described above, the close re-

Extensive investigations have confirmed a certain antagonism between cortisone and desoxycorticosterone [157]. Apart from its well-known effect in acute and chronic articular rheumatism, cortisone influences a great number of other disorders in which inflammatory processes are present with proliferation in the vascular connective tissue system as a result of excessive and pathologically enhanced mesenchymal reactions. The side-effects of cortisone have been repeatedly reported [137, 188].

In articular disorders of a mainly degenerative nature trials have been made of combined treatment with desoxycorticosterone and ascorbic acid. Such trials were indicated because cortisone differs c h e m i c a l l y from desoxycorticosterone only in the presence of an O group on the 11-C atom and an OH group on the 17-C atom [189, 190, 191, 192]. The actual mechanism involved in the b i o - c h e m i c a l processes taking place with this combined treatment has not as yet been completely clarified. Desoxycorticosterone a l o n e intensifies any inflammatory arthritic processes present. addition of a redox substance on the other hand (ascorbic acid, methylene blue, cysteine) inhibits them. According to personal communications [176] it may be supposed "that the adrenal cortical steroids act as part of an enzyme system, which catalyses a hypothetical hydrating or dehydrating metabolic reaction, in which ascorbic acid acts as a H donator or dehydroascorbic acid as a H acceptor. Whether this enzyme reaction can be transferred directly to the joint, possibly in association with hyaluronic acid metabolism, or whether (perhaps simultaneously) happenings localized in the cerebral cortex or diencephalon play a decisive part is still uncertain." Results of treatment so far have been most evident in chronic degenerative and deforming joint disorders (arthroses), in which inflammatory processes are either absent or only present in slight degree, pain has been alleviated and mobility and general condition improved. There appears to be no effect in inflammatory rheumatism

Central Nervous Organ (Diencephalon)

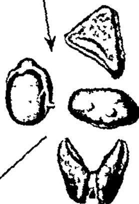


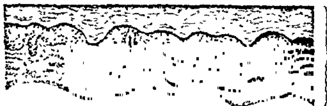
Anterior pituitary



Fig. 35
Schematic representation · Relations between central *nervous system, anterior pituitary, subordinate* endocrine *glands and* periphery of the body.

Subordinate endocrine glands





Periphery of the body

lationships between the adrenal cortex and the pituitary play a significant part. Figures 1 and 35 give a very simplified and schematic representation of extremely complicated processes. The functions of the adrenal cortex are regulated by the corticotropic hormone (ACTH) of the anterior pituitary. After pituitary extirpation, the failure of secretion of this corticotropic hormone leads to cortical atrophy with disappearance of lipoid, and to diminution of the thymus in size. There is also a connexion between the adrenal cortex and the gonadotropic hormones of the anterior pituitary. According to some authors, the excessive supply of gonadotropic hormones leads to hypertrophy of the adrenal cortex. On the other hand, in adrenalectomized animals the pituitary content in gonadotropic hormones falls [79, 196, 197, 198] Lactation is also said to depend on the presence of a functioning adrenal cortex [199, 189].

The relationship of the adrenal cortex to the gonads is established not only from the chemical standpoint, but also on clinical and experimental grounds [758, 759]. In Addison's disease, closely related to the severe metabolic disturbances, menstrual anomalies occur in women together with complete amenorrhoea and virilization. The presence of adrenal tumours leads to increased excretion of androgens in the urine, in children to premature puberty and in adults to heterosexual characteristics [79].

The progesterone-like effect of desoxycorticosterone acetate has also been the object of numerous studies [200]. According to the results of these studies, 5 to 8 mg of desoxycorticosterone acetate has the same action upon the rabbit uterus as 0.6 mg. progesterone; applied to the interior of the uterus, as little as 3 mg. desoxycorticosterone acetate suffices to transform the mucosa into the secretory phase [116, 201]. It is assumed that the corpus luteum of pregnancy secretes a substance resembling adrenal cortical hormones [202]. The significance of adrenal cortical hormones in infections and general intoxications has already been discussed [173, 203, 177, 181, 157] (see page 65).

Hormone treatment of many disorders with desoxycorticosterone acetate has proved correct; this preparation is however also becoming of increasing importance as an adjunct in treatment and after-treatment of many other diseases (infections, intoxications, damage to the liver parenchyma).

The changes in mineral and water balance, already set out in the *tables on page 64*, during treatment with desoxycorticosterone acetate deserve special mention because of the therapeutic consequences. On combined administration of desoxycorticosterone *and very high doses of salt*, with simultaneous potassium restriction, pathological retention of water occurs in animal experiments, with pulmonary oedema, circulatory disturbances and *hypertension* [204, 180, 205]. *The great significance of the repeatedly* stressed changes in salt metabolism is shown by the fact that adrenalectomized rats can be kept alive for long periods without cortical hormone, *simply by giving salt and lowering the potassium* content of the diet [375]. Conversely, salt deficit and excess of potassium in the diet have a lethal effect in adrenal cortical insufficiency. Small doses of salt in association with desoxycorticosterone diminish the need for hormone; on the other hand, large doses of salt induce undesirable side-effects. Hence the best results are obtained during treatment with adrenal cortical hormone if the diet contains sodium, chloride and potassium in the correct proportions to each other. Attention must always be paid to the diet during therapy with cortical hormones.

The property which desoxycorticosterone possesses of stabilizing the circulation has recently evoked some attention. It is of particular therapeutic use in circulatory dysfunction of vegetative origin [206, 207, 208, 209, 210, 749]. Capillary tonus is to a large extent regulated by desoxycorticosterone [211, 212]. This cortical hormone influences myocardial metabolism [213, 214], promotes myocardial recovery after contraction, and thus diminishes the fatigue of the heart [215]. If digitalis is given simultaneously, desoxycorticosterone enhances effectiveness of and tolerance to the latter [216].

The above description shows the enormous importance of the adrenal cortical hormones in physiological processes. A definitive assessment of all the functions of the adrenal cortex is as yet impossible. However, we already know of *many possibilities for* the therapeutic employment of desoxycorticosterone acetate.

I. Gonadotropic Hormones:

1. Follicle-stimulating hormone (FSH), or Follicle-ripening hormone Gonadotropin I Gametogenic hormone Gametokinetic hormone *Thylakentrin*	**2. Luteinizing hormone (LH), or** Luteotropic hormone Corpus-luteum maturing hormone Gonadotropin II ICSH (interstitial-cell-stimulating hormone) *Metakentrin*	**3. Prolactin (PH), or** Luteotrophic hormone (LTH) Luteotrophin Lactation hormone Lactogenic hormone Galactin Mammotropin

II. Metabolic Hormones:

4. Corticotropic hormone ACTH (adrenocorticotrophic hormone) Adrenocorticotropic hormone Corticotropin Adrenotropic hormone Adrenocorticotropin Adrenotropin	**5. Thyrotropic hormone (TTH)** Thyrotropin TSH (thyroid stimulating hormone)	**6. Growth hormone** Somatotropin Somatotropic hormone STH (somatotrophic hormone) Chondrotropin

Only the anterior pituitary hormones will be dealt with in this monograph, partly on account of their close relationship to the gonadal and adrenal cortical hormones. These anterior pituitary hormones are chemically proteins or proteids. Growth hormone, prolactin and the corticotropic hormone are simple proteins. On the other hand, thyrotropic hormone, follicle-stimulating hor-

Chemistry, Physiology and Pharmacology of the Tropic Hormones of the Anterior Pituitary

General

The hormones formed by the pituitary are designated as p r o t e o hormones in contrast to the s t e r o i d hormones [79]. They are either proteins or their degradation products, and are further degraded to inactive substances by the corresponding digestive enzymes which split peptides. The pituitary forms two varieties of hormone. One variety has an independent function in the body. By means of the other, the pituitary regulates subordinate endocrine glands: the second type is therefore known as tropic and trophic hormones. Tropic hormones are those whose proven effect on a subordinate organ it is desired to indicate in this way (see Figs. 1 and 35). On the other hand, trophic hormones are those whose effects have usually been shown on close study to be via indirect mechanisms [217]. Out of the many pituitary hormones whose presence has been postulated on the grounds of observed physiological effect, chemical study of the pituitary has revealed up to now 9 or 10 in a state of purity. Of these 6 come from the anterior lobe (see Scheme on page 77). They are the three g o n a d o t r o p i c hormones – follicle-stimulating hormone, luteinizing hormone or luteotropic hormone, and prolactin or luteotrophic hormone – and three m e t a b o l i c h o r m o n e s – corticotropic hormone, thyrotropic hormone and growth hormone. The pars intermedia contains pigment hormone In the posterior lobe, oxytocin, with an effect on the uterus, vasopressin, with an effect on blood pressure, and the antidiuretic hormone adiuretin have been demonstrated.

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mone and luteinizing hormone are glucoproteids, as are also similar hormones formed by the placenta, i. e. the gonadotropic hormone contained in human pregnancy urine (chorionic gonadotropin) and the serum gonadotropin in the blood of pregnant mares. All protein-like anterior pituitary hormones are heat-labile in solution, with the exception of corticotropic hormone, which undergoes a certain amount of degradation without loss of activity. All the anterior pituitary hormones in solution at room temperature will keep only for a very limited time. As mentioned above, all the pituitary hormones are more or less rapidly inactivated by peptic and tryptic digestion. For this reason, no effect need be expected after oral administration. They must be administered parenterally. On account of their protein character, synthesis of pituitary hormones has not so far been achieved. Production of pituitary hormones is therefore only possible from animal pituitaries. This basic material is unfortunately available only in very limited amounts, and is correspondingly very expensive. For this reason, the pituitary is employed usually only for the production of corticotropic hormone (ACTH "Schering A. G. Berlin"), of thyrotropic hormone (Primothyron) and of growth hormone. On the other hand, pituitary itself is not suitable for the technical production of gonadotropic hormones, because of the extremely small amounts of gonadotropic material present in it. Because certain chorionic gonadotropic hormones formed in the placenta have the same type of action, it is customary to use as the point of departure for preparation of concentrated substances either the urine of pregnant women (chorionic gonadotropin, Primogonyl) or the blood of pregnant mares (serum gonadotropin, Prantin). However, even pregnancy urine and mares' serum are not available in unlimited amounts.

Various biological methods are used for the testing of these gonadotropic substances [175, 79, 22]. For example, one international unit (i. u.) of serum gonadotropin corresponds in effect to 0.1 mg. of an international standard preparation.

Because of the considerable degradation which takes place in the digestive tract, oral administration of gonadotropic hormones is useless, since as mentioned above they are rapidly inactivated by peptic and tryptic digestion. On the other hand, if they are injected intramuscularly these agents are quickly and completely absorbed.

According to the total effect of individual anterior pituitary hormones, a distinction can be made between two principal groups: *gonadotropic hormones* and *metabolic hormones*, such as corticotropic and thyrotropic hormones and the growth hormone.

The Gonadotropic Hormones

The gonadotropic anterior pituitary substances and similar hormones of placental origin have a regulating function as *supervisory sex hormones, and are themselves regulated and coordinated* by superior regulating mechanisms in the nervous system. They regulate the development and function of the male and female sex glands, and hence also the development and function of the secondary sex characters. The metabolic actions of these hormones only appear as side-effects. Follicle-stimulating hormone stimulates the growth of the granulosa cells in the follicles *of the ovary, but does not induce secretion of follicular hormone.* The latter occurs only under the influence of small supplementary amounts of luteinizing hormone, which completes maturation of the follicle and also brings the theca cells to luteinization. Before puberty, both hormones are secreted only in such amounts as to ensure production in the ovary of the child of the very small quantities of follicular hormone necessary for the physical and mental development of the growing girl. As the child grows older, the sensitivity of the central regulating apparatus to the level of oestrogen in the blood diminishes; at puberty, there is greater secretion of both hormones, the follicle-*stimulating and the luteinizing. As a result the first completely* mature follicle is formed. Apparently induced by the rise in oestrogen secretion, a secretion of prolactin now begins in the pituitary and there is also secretion of progesterone by the mature corpus luteum.

Because of its influence in promoting growth of interstitial tissue in the testis, luteinizing hormone is also called the "interstitial-cell factor." However, no manufacturing process so far has successfully separated follicle-stimulating hormone completely from luteinizing hormones All commercial preparations therefore contain mixtures of both. Chorionic gonadotropin from the urine of pregnant women is effective only if the pituitary is functioning, on the other hand, serum gonadotropin from the blood of pregnant mares is still effective even after hypophysectomy, at least for a short time. Gonadotropic hormones are not sex-specific; they have an effect on b o t h sexes.

Administration of gonadotropic substances to women leads, via follicle-stimulating hormone, to hyperaemia and increase in weight of the ovaries Follicles mature in favourable cases, and are transformed after rupture into corpora lutea under the influence of luteinizing hormone. With the passage of time the increased formation of follicles and corpora lutea leads to an increased output of the hormones formed in the ovaries, and secondarily to the specific changes in the sex organs due to these hormones and described on pages 29 and 31. In the male, the follicle-stimulating factor increases spermatogenesis (generative effect) and the luteotropic factor the growth and activity of the testicular interstitial tissue. As a result of the latter, hormone production increases and an enhanced development of the secondary sex characters begins. The effector organ for gonadotropic hormones is the ovary or the testis If the gonads are lacking, gonadotropins are ineffective, as already stressed.

The most common form of functional change in the anterior pituitary is found at the climacteric, at which following the disappearance of follicular hormone a release phenomenon occurs, with resulting overproduction of gonadotropic hormones. Hormone production in the pituitary is s p e c i a l l y regulated because not all its hormones are needed in equal amounts at all ages and in all situations. Thus growth hormone is formed in

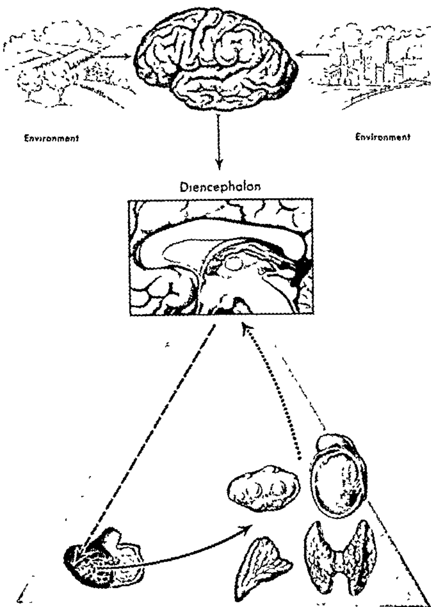
of the pituitary and on the entire organism is readily explicable (cf. Fig. 37).

A stimulus proceeding from the periphery passes through the autonomic nervous system to the diencephalon and thence to the pituitary; from the latter, glandular activity is regulated by endocrine means through secretion of tropic hormones. These relationships are very complicated, and make diagnosis and therefore the planning of treatment very difficult for the doctor. This many-sided mechanism of action, involving both autonomic nervous system and internal secretions, can be clarified by the following examples.

It is well-known that during the corpus luteum phase of the endometrium (secretory phase) vagotonic manifestations appear (spasms, leucorrhoea, constipation). Oestrogen counteracts these vagotonic manifestations (e. g. favourable effect on gastric ulcer). Conversely, purely nervous stimuli affect the activity of the gonads (amenorrhoea due to arrest in wartime) [376]. As a result of nervous impulses, disturbances of follicle maturation occur, and finally atrophy of the entire ovary may take place.

These examples show the close relationship of genital function to the autonomic nervous system. Disturbances of the balance between the sympathetic and the parasympathetic lead to deviations of endocrine function [377, 378], conversely, pathological processes in the endocrine system affect vegetative function. All these impulses are controlled by the functional *cooperation* of the pituitary and the diencephalon. *Dysregulation in this system, especially with enhanced effect of oestrogen (hyperfolliculinism), may provoke a series of well-known pathological signs and symptoms (e. g. migraine, amenorrhoea, angiospasm, tachycardia, vasolability).*

The fact that this *mechanism is frequently not taken into account sufficiently in the choice of hormone therapy explains the failure of much of this type of treatment.*



The physiological regulations of the output of tropic hormones from the anterior lobe of the pituitary for ovaries, testes, adrenals and thyroid gland

Fig 37

In cases of disease, signs of deficiency and of overactivity of the regulating centres in the diencephalon may also appear; hence, many clinical observations may be clarified by a knowledge of the regulating apparatus described above. The significant association of humoral and nervous control is not limited to the anterior pituitary-diencephalon system. It is also found in the case of the secretion of posterior-lobe substances and the pigment hormone of the pars intermedia.

The Aschheim-Zondek pregnancy test and the Galli-Mainini toad or frog test are based on the appearance in the urine of pregnant women of chorionic gonadotropins [380, 381, 382, 383] (see also page 154). Quantitative determination of pituitary gonadotropins in the urine is of clinical significance in the diagnosis of a basophil adenoma of the pituitary, disease of the hypothalamus, and certain ovarian tumours [42].

Metabolic Hormones

Adrenocorticotropic Hormone

The most significant metabolic hormone of the pituitary is the corticotropic hormone ACTH (adrenocorticotropic hormone). The importance of corticotropic hormone in all vital processes is clearly shown by the fact that the adrenal cortex, whose internal secretion is controlled by corticotropic hormone, is the only v i t a l l y s i g n i f i c a n t endocrine gland influenced by the pituitary A humoral effect of the pituitary on adrenal cortical activity was demonstrated as early as 1926 [280]. In 1942 the factor responsible for this effect was isolated; this is the adrenocorticotropic hormone of the anterior pituitary, now commonly known as ACTH [281, 282, 283].

As already stated, ACTH is a protein derivative, a polypeptide with a molecular weight of about 20,000 and an isoelectric point of 4.7—4 8. Since its chemical structure has so far not been elucidated, ACTH can as yet not be prepared by synthesis. It is chiefly obtained from the pituitary of the pig [284], sheep, cattle [285] or whale [286]. The degree of purity of the different ACTH preparations used nowadays in therapy varies greatly For this reason, the habit still in vogue of labelling ACTH preparations in mg. gives no objective standard of effectiveness. Trials have shown that ACTH "Schering A G Berlin" is one of the purest preparations so far put on the world market. It is practically free from posterior pituitary substances, and contains no admixture of gonadotropic substances or of thyrotropic or growth hormone ACTH is water-soluble; in contrast to the other anterior pituitary hormones, it is heat-stable, and it is destroyed in vitro by strong acids and by peptic [282, 287] and tryptic [288] action.

For this reason, it is inactive on oral administration, in contrast to cortisone [289]. It is probable that the effect of ACTH is less dependent on an intact protein molecule than on a certain type of peptide structure [217].

ACTH is probably formed in the basophil cells of the anterior pituitary [290, 291]. It has only a very limited period of action in the organism (about 4 to 8 hours). It is no longer demonstrable in the blood stream 15 minutes after an intravenous injection [292, 293]. In the urine of adults ACTH cannot be demonstrated, even after injection of large doses. Studies of ACTH labelled with radioactive iodine have shown that after intracardiac injection the hormone is immediately demonstrable in the adrenal cortex, but rapidly disappears again out of the latter [291]. In the organism, ACTH is probably destroyed by the liver, the kidneys and the adrenals [290]. Secretion of ACTH by the anterior pituitary occurs as soon as the blood concentration of adrenal cortical hormones is low. During the "alarm reaction" in the adaptation syndrome (see page 67), ACTH secretion is mobilized by neural and endocrine mechanisms [183]. The most recent experimental work has shown that adrenaline is essential for the functioning of this controlling mechanism [295, 296, 297, 298]. Even quantities of this adrenal medullary hormone so small as not to alter the blood sugar level will stimulate formation and output of ACTH in the anterior pituitary, in the presence of increased demands on the organism. Neural (neurosecretory) regulation via hypothalamic centres also appears to be of essential significance as regards secretion of ACTH, since in animal experiments section of the nerve paths from the diencephalon to the pituitary prevents the response of increased output of ACTH to exogenous stimuli [299]. Under extraordinary stress, considerable quantities of ACTH may be produced by the human pituitary within a short space of time [290, 300, 292]. This overproduction of ACTH during the alarm reaction is always at the expense of all the other hormones formed by the anterior pituitary [184, 185].

The total effect of ACTH depends on the reactivity of the adrenal cortex. It stimulates the latter to secretion of its various steroid hormones, particularly the 11-hydroxycorticosteroids (cortisone and, according to recent work, chiefly compound F) [301, 302, 303, 285, 304, 305]. On the other hand, administration of ACTH has no effect on adrenalectomized animals. This behaviour shows that the effector organ for ACTH is exclusively the adrenal cortex. Thus, if the adrenal cortex is non-functioning or absent, the hormone is unable to produce physiological or therapeutic effects.

There are a whole series of qualitative and quantitative techniques for testing the effectiveness of ACTH [284, 306, 307, 308, 309, 310, 311, 44, 312, 281, 313, 314].

Three procedures are principally used at present, all of them being carried out on hypophysectomized rats.

1. **The maintenance test:** Weight and normal morphological structure of the adrenal cortex can be maintained constant in 40-day-old, hypophysectomized test animals with a total of 0.2 mg ACTH [313].

2. **The repair test:** The sudanophobe zone (no longer staining with Sudan orange), which forms in the adrenal cortex of test animals after hypophysectomy as a result of impoverishment in cholesterol, can be made to disappear again by giving 0 01—0.025 mg ACTH [313, 281].

3. **The vitamin-C test:** The ACTH content of the test substance can be inferred from the degree to which the substance lowers the ascorbic acid content of the adrenal cortex of test animals [308].

Standardization:

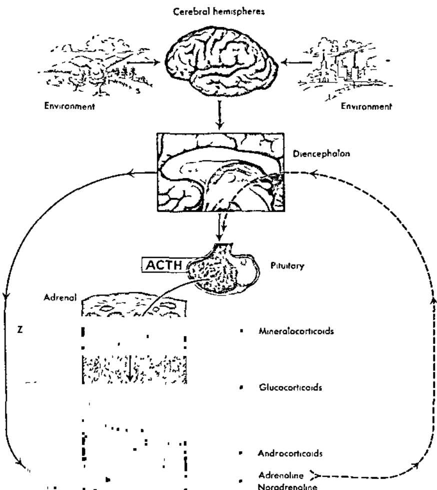
The effectiveness of ACTH "Schering A. G Berlin" is determined by the procedure of Sayers et al (ascorbic acid depletion of the adrenal cortex of hypophysectomized rats), and expressed in international units (i. u.). One i u corresponds to the effect of

1 mg. of an international standard ACTH preparation. Preparations with a higher degree of purity than the international standard (such as ACTH "Schering A. G. Berlin") obtain the effect of one i. u. with less than one mg. of substance [750]. One U. S. P. unit of corticotropin (United States Pharmacopoeia) is identical with an i. u. ACTH [315].

For clarification, the many effects of ACTH on the total metabolism of the organ are grouped below according to the metabolic subdivisions. Detailed descriptions of the physiological effects of ACTH with comprehensive bibliographies on all special questions will be found in the reviews [303, 285, 316, 317, 318, 319, 217, 290, 750].

Adrenal cortex:

Administration of ACTH leads to a morphologically demonstrable hypertrophy of the adrenal cortex [309, 310], principally due to increased growth of the zona fasciculata in whose cells the 11-hydroxycorticosteroids are formed [290]. The manifest expression of this increased secretion in the adrenal cortex is the raised excretion of 17-ketosteroids and 11-hydroxycorticoids in the urine (see page 204 and Fig. 38). Conversely, administration of cortisone causes an initial fall in 17-ketosteroid excretion, and on longer employment a reversible atrophy of the adrenal cortex. The observed increase in 11-hydroxycorticoid excretion after administration of cortisone is simply to be ascribed to the *increased supply* of cortisone, an 11-hydroxycorticoid. Cortisone also inhibits production and output of ACTH in the anterior pituitary, thus causing a secondary hypofunction of the adrenal cortex. With ACTH therapy, all these dangers of cortisone therapy are absent. ACTH lowers the content of the adrenal cortex in vitamin C (adrenal cortical function test!) [308] and in cholesterol (the mother substance of corticosteroids) [314, 320]. On the other hand, the glycogen content of the adrenal cortex rises



The endocrine relationships between cerebrum, diencephalon, pituitary and adrenals

Fig. 38

Other endocrine glands:

As a result of inhibition of the thyrotropic [321] and gonadotropic [285] functions of the anterior pituitary by ACTH, the activity of the thyroid and the gonads is reduced. Because the amount of adrenal cortical hormones circulating in the blood is increased during ACTH treatment, the metabolic effect of thyroxine is however enhanced [322]. The antidiuretic function of the posterior pituitary is also inhibited, so that polyuria may occur. The hyperglycaemia resulting from the effects of ACTH leads to a reactive rise in function of the pancreas with augmented output of insulin. Since the latter continues some time after the cessation of the ACTH effect, a hyperglycaemic state may appear after ACTH has been discontinued. The changes in the secondary sex characters observed after large doses of ACTH (e. g. hirsutism) are ascribed to increased production of androgens in the adrenal cortex, and maybe also of testosterone in the testes. Because ACTH diminishes the effect of the anterior pituitary growth hormone, there is inhibition of osteogenesis and chondrogenesis [323]. For this reason, ACTH treatment is contraindicated in the presence of osteoporosis and osteomalacia.

Protein metabolism:

A metabolic phenomenon which is readily demonstrable in man, and can also be used as a test for ACTH effect during treatment, is the relation of uric acid to creatinine excretion, the so-called "uric acid/creatinine quotient" [311]. ACTH causes an initial rise in the excretion of uric acid [324], which may continue until there is an excess of uric acid over creatinine of 70—200% without increased formation of uric acid in the body. The uric acid excretion later returns to normal values In the presence of adrenal cortical *hypofunction*, this displacement of the uric acid/creatinine quotient does not occur [290]. As a result of increased neoglucogenesis (new formation of *carbohydrate from protein and* fat) and the associated degradation of protein due to ACTH

action, there is a rise in nitrogen excretion [325]. The nitrogen balance becomes negative. The amino-acid content of the blood is raised [284]; the albumin/globulin ratio rises because of diminution of gamma-globulins and fibrinogen [326]. In cases of inflammation ACTH usually leads to return to normal of the albumin/globulin ratio [751] and hence to a fall in the erythrocyte sedimentation rate.

Carbohydrate metabolism:

Through its influence on production of glucocorticoids, ACTH is ultimately responsible for the constant level of glycogen in the liver and muscles. If glycogen requirement is raised, it brings about an increase in glycogen deposition in the liver by augmenting neoglucogenesis [325]. By its stimulating influence on carbohydrate metabolism, ACTH enhances mental energy and physical efficiency [327 328 329 330]. ACTH simultaneously lowers the carbo hydrate tolerance of the organism, because of this hyperglycaemia and glycosuria may arise [331]. The glycosuria may however be ascribed in part to the diminution in reabsorption of glucose from the kidney tubules due to ACTH [332]. In certain circumstances, ACTH causes inadequate carbohydrate utilization in the tissues. This diminution in sugar utilization at the periphery is associated with a simultaneous rise in fat mobilization, which further spares the carbohydrate reserve [285].

Fat metabolism:

Deposition of fat in the organism is favoured by increased mobilization and better utilization of fat The blood content in phosphatides rises [333], but on the other hand the cholesterol and neutral fat values in the serum fall [285] Mobilized fat is also in part transformed into carbohydrate in increased amount. ACTH causes ketonuria in healthy persons and to a greater extent in diabetics [334].

Mineral metabolism:

Extensive changes in *electrolyte balance appear during ACTH* treatment. In particular, fairly large doses cause retention of water, sodium and chloride in the tissues. It is therefore advisable to limit the intake of fluid and salt during long-continued ACTH medication. ACTH also causes a fall in the potassium, chloride and phosphate values in the blood [326], so that a hypokalaemic and hypochloraemic alkalosis may appear, with muscular weakness and great fatigue [319]. For the prevention of this during treatment with large doses of ACTH, oral administration of 2—3 g. potassium chloride daily is indicated. The excretion of potassium, calcium and phosphate in the urine is significantly raised [371, 303].

Blood and tissue cells:

The changes in the blood picture under the influence of ACTH are of particular importance [335, 336, 337, 338, 290, 319, 339, 340]. In the circulating blood there is a very rapid and definite fall in eosinophil values, and these cells *frequently disappear completely. The* number of lymphocytes is also greatly diminished. Conversely, there is an increase in neutrophil granulocytes. The thrombocyte count is also increased [341, 318, 285]. In addition, ACTH leads to a rise in reticulocyte values and an increase in phagocytic activity of leucocytes and of cells of the reticulo-endothelial system (histiocytes, macrophages) [235, 183, 342, 318]. The sudden "*fall in the eosinophil count*" under the influence of ACTH is so characteristic that it has been introduced into clinical practice as a test for the effectiveness of ACTH, and simultaneously as an *indicator of the functional capacity of the adrenal cortex, under* the name of the "Thorn test" [44, 343, 344, 345, 346]. If after injection of 25 i. u. ACTH the eosinophil count in the peripheral blood does not fall by at least 50% within 4 hours, it may be concluded that *adrenal cortical function is below normal*. For more accurate assessment of the eosinophil count, which varies greatly with the individual and the time of day, it is advisable to employ

a special counting method [317, 318]. After prolonged treatment with very high doses of ACTH, atrophy of the red bone marrow with secondary fatty change is demonstrable [323].

ACTH has a powerful inhibitory effect on lymphatic tissue. It causes involution of the thymus and lymph nodes, as well as signs of dissolution in the lymphocytes. This ACTH effect may amount to a far-reaching dissolution of lymphatic tissue [290, 285, 319, 183].

In view of the special effectiveness of ACTH in all diseases of the connective tissue associated with tissue proliferation and inflammatory processes, the actions of this hormone on mesenchymal tissue are of the greatest importance. In an organism capable of reacting, ACTH inhibits tissue proliferation, and especially fibroblast growth [350, 351, 352, 353 285, 318] Formation of granulation tissue is delayed, and in consequence wounds heal less easily and tissue regenerates less, e. g. in fractures [354, 355, 356, 357 358]. ACTH therapy inhibits the general capacity of the mesenchymal cell system to react Its cell metabolism is lowered, the processes of cell division are inhibited, and pathologically excessive proliferation of mesenchyme is arrested ACTH causes an increased output of the cortical hormones cortisone and compound F, which are now regarded as "endogenous mitotic poisons" required by the organism for the regulation of cell construction and destruction [350 351] The inhibition of pathological proliferation of connective tissue makes an essential contribution to the antiphlogistic effect of ACTH Inhibition of mitosis is not a general effect, since it affects ectodermal and mesodermal tissue but not endodermal tissue [350]. The more undifferentiated the proliferating tissue, the more powerful its inhibition by ACTH [350]

Enzyme system:

Pepsin formation in the stomach and production of gastric mucus are increased by ACTH provided that the gastric mucosa is func-

tioning [285]. Excretion of uropepsin in the urine rises [359, 360]. Hydrochloric acid secretion by the stomach remains unaffected. The arginase content of the liver and kidneys rises. The glutathione content of the blood diminishes [361, 362, 363]. The possibility of preventing ACTH hyperglycaemia and glycosuria by giving glutathione is of therapeutic importance [285]. Because the sulphydryl system in the skin is inactivated, ACTH may lead to increased pigmentation (melanin deposition) [285]. Large doses of ACTH also raise the serum peptidase values [364] and inhibit the tissue effect of acid phosphatases [365].

The complex influence of ACTH on the hyaluronidase-hyaluronic acid system is of particular interest nowadays. After ACTH treatment, disappearance of the mast cells which produce hyaluronic acid and loss of tissue hyaluronic acid were demonstrated in tissue sections [325]. Pathological formation of hyaluronic acid (e.g. in rheumatic affections of the joints) is said to be normalized by ACTH

The antihyaluronidase content of blood serum is diminished [366, 367], in certain circumstances ACTH lowers the effect of hyaluronidase [368, 369, 370, 371, 372]. The inhibiting effect of ACTH on the action of lysozyme is of therapeutic significance in ulcerative colitis, since the enzyme appears in excess in this condition [285, 360].

Immune-biological factors:

The whole of the allergic process is profoundly influenced by ACTH. The situation of the body as regards immunity may be completely altered. ACTH at first causes a transient rise in antibody content of the blood. When the effect of ACTH is more prolonged however, blood antibodies are diminished. The antigen-antibody reaction is inhibited [285, 304]. Because of this, equilibrium attained between the most varied pathogens and the organism may be disturbed, and an acquired immunity may be lost. The consequence of this is often an activation of chronic infection

(danger of exacerbation of tuberculosis). Because ACTH inhibits histamine formation and increases histaminase activity, anaphylactic shock may be suppressed or mitigated [285]. By activation of the reticulo-endothelial system, ACTH also leads to increased destruction of histamine [318].

Mental effects:

ACTH treatment usually has a definite effect on the mental behaviour of the patient. An obvious euphoria commonly occurs at first, but with more prolonged treatment or sudden withdrawal of the hormone this may change into a state of depression. Changes in the electroencephalogram under the influence of ACTH have been described [373]. ACTH also has an anaesthetic effect [285].

Thyrotropic Hormone

By administration of thyrotropic hormone, even to human subjects, all those effects are obtainable which can be achieved with doses of thyroid hormone. Thyrotropic hormone (TTH) of the anterior pituitary, available to the physician as Primothyron, stimulates the function and growth of the thyroid gland The glucoprotein TTH gives the usual protein reactions, is not dialysable and not ultrafiltrable. In its preparation from animal pituitary TTH can now be completely separated from the other anterior pituitary hormones. A healthy human pituitary with a fresh weight of about 0.6 g contains only about 5—30 G P. units of thyrotropic hormone [218] Primothyron contains TTH in highly purified form. This TTH preparation is practically free from posterior pituitary substances and from follicle-stimulating, luteinizing and growth hormones; it is also free from admixture of adrenocorticotropic hormone.

Because proteolytic enzymes destroy TTH, it is rendered inactive immediately on oral administration. TTH is to a large extent inactivated by brief exposure to a temperature of over 60° C.

and completely destroyed by boiling. A freshly prepared solution of TTH retains its effect for about 3 weeks under sterile conditions at room temperature, whereas the dry hormone will keep *practically indefinitely*.

Removal of the pituitary from dogs leads to atrophy of the thyroid [219]. Conversely, extirpation of the thyroid leads to hypertrophy of the pituitary [220]; this becomes more marked as time goes on after thyroidectomy [221]. The thyroid atrophy after removal of the pituitary, and all the deficiency signs (lowered basal metabolism, fall in blood iodine value, drop in body temperature), can be prevented or completely overcome by administration of TTH [222]. After administration of TTH the epithelium of the thyroid follicles proliferates; the cells become cubical or cylindrical and the epithelium *multilayered*. *Granulation* and vacuolization of the protoplasm appear, as well as loosening of the chromatin skeleton of the cell nuclei. The protoplasm, which is neutrophil in the resting gland, becomes more basophil. Other typical findings are the appearance of numerous mitoses in the epithelium, the disappearance of colloid, and the enhanced blood supply to the whole organ. A certain enlargement of the thyroid gland is also commonly observed [17]. The extent of the changes depends on the quantity and duration of hormone supply. The reactions described appear astonishingly early, even within 1/2 to 2 hours of administration of TTH [223].

There are direct and indirect techniques for determination of TTH. With the indirect technique, signs are measured which are due to thyroid activation by TTH (e. g measurement of the increase in basal metabolic rate [224], the diminution in liver glycogen, the rise in resistance of the mouse to acetonitrile, etc.) *Direct methods*, which evaluate the increase in weight of the thyroid or its histological changes, are however more reliable [17, 225]. Since the guinea-pig is the most sensitive of all animals to TTH administration, *it is now used for standardization of* thyrotropic preparations. Histological procedures produce the

most reliable results as regards determination of thyrotropic effect [17]. The substance to be studied is injected subcutaneously on 3 successive days into guinea-pigs of 100—150 g. body weight. kept under constant experimental conditions to eliminate all thyroid changes due to external influences. The experimental animals are killed on the fourth day, their thyroids histologically examined, and the effectiveness of the TTH expressed according to the histological findings in guinea-pig units.

One guinea-pig unit (G. P. U.) of TTH, according to Junkmann and Schoeller, is the smallest quantity of the hormone, which on injection on 3 successive days into infantile guinea-pigs weighing 100—150 g. produces on the 4th day in 50% of the animals treated the characteristic histological changes in the thyroid (proliferation of follicular epithelium, increased mitosis, disappearance of colloid).

In 1932, thyrotropic hormone free from other agents was isolated successfully from animal anterior pituitary, and in 1939 it first became possible to introduce the TTH preparation Primothyron into therapy [17, 226, 227]. Since the only effector organ for TTH is the thyroid, it can develop its action only if this gland is present and capable of function. After thyroidectomy, TTH is ineffective [228]. The following are the detailed effects of TTH. Because the thyroid is activated, there is a very rapid rise in basal metabolism (in the guinea-pig even on the first day) [228, 229]. Quantitative relationships are demonstrable between the dose of the hormone and the rise in metabolic rate. Basal metabolism may be raised by 35% or more [224, 229, 230]. It is noteworthy that this rise in basal metabolism occurs much earlier with TTH and to a greater degree than with administration of thyroid hormone. The metabolic rise takes place more rapidly in subjects with goitre than in healthy individuals. Administration of large doses of TTH leads to diminution of liver glycogen [231]; this impoverishment in glycogen can be readily compensated by insulin. The muscle depots of glycogen are on the other hand scarcely af-

7*

fected. The iodine content of the thyroid, and especially its thyroxine content, diminishes after administration of TTH. Iodine values in the thyroid may sink to 1/10 to 1/20 below normal. This is associated with a rise in iodine content in the blood, specially affecting the organically-bound iodine, and a parallel rise in iodine excretion in the urine [232, 233, 234, 235, 236]. In human subjects after treatment with thyrotropic hormone the blood iodine level rises to a threefold value [234]. The increased amount of thyroid hormone poured out under the influence of TTH into the blood is difficult to demonstrate, since it is rapidly diluted greatly by the blood stream and excreted. After TTH administration there is also an increase in diuresis, with rise in salt and urea excretion, rise in calcium excretion via the bowel, and increased creatinuria [237, 238, 239, 240]. Changes in myocardial metabolism [241, 242], rise in pulse rate, and rise in body temperature, increase in the amount of circulating blood and rise in alkali reserve in the blood have all been demonstrated [243, 244]. Definite exophthalmus was first produced experimentally with certainty by giving very large doses of TTH; this had not been possible with administration of thyroid hormone [245, 246]. The TTH effects on the adrenal cortex formerly described are now attributed with certainty to admixture of adrenocorticotropic hormone in the preparations first made.

Every fall in the level of thyroid hormone in the blood causes increased production and output of TTH. On the other hand, increase in thyroid hormone in the blood has a definite inhibitory effect on the production and secretion of thyrotropic hormone in the anterior lobe of the pituitary [247, 248, 249, 250]. Administration of thyroxine and diiodotyrosine, like increased output of the naturally occurring thyroid hormone, finally leads to inhibition of the thyrotropic function of the anterior pituitary, and thus to a resting condition and atrophy of the thyroid gland [251, 252, 253 254]. Recent studies with radioactive iodine have shown that TTH promotes the capacity of the thyroid to store iodine [255, 256 257].

Increased iodine storage by the thyroid during TTH therapy seems to depend on whether the thyroid has previously been completely freed from the iodine store present in it [258]. Thyroid colloid contains a proteolytic enzyme, which is distinctly increased after treatment with thyrotropic hormone [259, 260 261, 262]. By means of this enzyme, the large thyroglobulin molecule which acts as the carrier of thyroid hormone in the follicular colloid is degraded into polypeptides and peptones [263], this being the way in which thyrotropic hormone promotes secretion of thyroid hormone The same enzyme can also promote synthesis of thyroglobulin [259, 260, 261, 262]. It is probable that TTH, after its effect on the epithelial cells of the thyroid is again inactivated by the endocrine iodine present in the gland [264, 265, 266]. TTH is demonstrable in the blood only in very small amounts; on the other hand, its excretion in the urine of healthy individuals can be shown. Conversely, there is no TTH in the urine of patients with thyrotoxicosis [267].

The increase in function of the thyroid cannot usually be maintained for an unlimited period by continuing to give the s a m e doses of TTH [229, 268]. With the continued action of thyrotropic hormone, a countermechanism is evidently set in motion to prevent the appearance of thyrotoxic manifestations. The phase of thyroid stimulation is succeeded by a refractory phase. Macroscopical and microscopical changes in the thyroid gland gradually regress with prolonged treatment with thyrotropic hormone [269, 17, 239 270, 271, 272]. The increase in metabolic rate also subsides with continued administration of TTH, the basal metabolism in some cases falling below normal, and the glycogen content of the liver returns after a previous fall to its original values [273 274]. This regulating mechanism is of great importance in therapy with TTH. Because of it, continued dosage with TTH at the same level can never produce thyrotoxicosis, as in thyroxine treatment. However, this refractory stage can be overcome by continuously increasing the dose of hormone [273] The further increase in

thyroid function thus obtained again provokes an increase in "protection" against the effect of thyrotropic hormone. The presence of the thyroid gland is necessary for the appearance of this protective mechanism. It does not appear after thyroidectomy, but reappears after administration of thyroxine. The protective action may be enhanced by simultaneous administration of thyroxine. It has not yet been established whether the refractory behaviour of the organism on prolonged treatment with TTH is due to a true antihormone formation [275, 276, 277, 278], or depends upon formation of an antigen to the protein compounds coupled to the thyrotropic agent [279].

The Growth Hormone

The growth hormone is apparently of importance in later foetal life and during the growth period of the child. Its effect is extinguished when the epiphyses unite under the influence of the thyroid and the parathyroids. The output is said to diminish with the appearance of increased gonadotropin secretion at puberty. With some growth-hormone preparations, therapeutic results have been obtained in disturbances of human growth, and gigantism has been produced in animals. Further knowledge of the effects of growth hormone on protein metabolism suggests future therapeutic indications.

The Use of Hormones in General

It must be repeatedly stressed that hormones must not be used without selection, or in random dosage. A dosage adapted to the individual organism is of decisive importance for success. The latter also depends to a large extent on the preparation employed. The differences which may arise from use of different forms of administration of a preparation are shown by the following example. If in infantile castrated rats the weight of seminal vesicles per 100 g. of rat is compared after experimental administration of 0.45 mg. testosterone or testosterone propionate, over 6 days, the following significant figures are obtained

After.	Seminal vesicle weight per 100 g body weight
Injection of testosterone propionate intramuscularly (Testoviron i. m) . . .	405 mg.
Inunction of testosterone in alcoholic solution (Testoviron T transcutaneously)	355 mg.
Inunction of testosterone in oily solution	53 mg.
In:	
Untreated controls	25 mg

The following differences as regards effect were found by comparison of various oestrogen preparations Progynon (oestradiol) has 5 to 8 times as powerful an action as oestrone. Progynon B oleosum intramuscular (oestradiol monobenzoate) has a more protracted effect than oestradiol (Progynon). Progynon C by mouth (ethinyl oestradiol) is about 10 times as effective as Progynon B oleosum intramuscularly One tablet of Progynon C corresponds as regards effect to 3 Progynon dragees forte or 15 Progynon dragees.

These *different degrees of effect explain* the great differences in dosage of individual preparations. For example, to produce a full proliferative phase in the endometrium of a complete castrate it is necessary to give 5 doses of 5 mg. Progynon B oleosum forte in 20 days, but only about 1.7—2.5 mg. Progynon C in *16—20 days* [384, 385]. These comparisons *illustrate* the need for careful differentiation of dosage of various preparations (see page 152).

In hormone therapy, as so often in drug therapy, the guiding principle is that during a certain period of time a certain blood level must be reached and maintained. A regular supply of hormone at intervals which have been determined by clinical experience is the prerequisite for success. A better effect may be expected by administration of divided doses at short intervals than *by less frequent medication. Administration of small or* medium doses usually has a stimulating effect on the effector organ. Conversely, the administration of large doses of oestrogen or testosterone may in certain circumstances *lead* to an opposite action because of inhibition of controlling centres (cf. Fig. 36a), and also produce damage or undesired side-effects. Hence dosage schedules valid in every case are usually impossible to draw up. The size of dose and its effects have been shown by experience to undergo *wide individual variation. It will often be necessary* by trial in any case to ascertain an individual dose with optimal effect.

In the early days of hormone therapy attempts were made to overcome deficiency signs of endocrine origin by implantation (transplantation) of animal glands. This technique was shown to be generally unsuitable for various reasons. According to the *age of the animal*, its general condition, and the time at which the gland was removed, these transplants secreted varying quantities of hormone. The site of implantation usually healed up, but the transplant was *rapidly absorbed, so that only an* unknown, small amount of hormone was supplied to the body over

a short period. As a rule, hormones are not stored in the glands themselves. On the other hand, even and exact effects may be expected from pure hormone preparations Standardization in international units (i. u.) or on mg. led to the establishment of reliable dosages with exactly comparable actions.

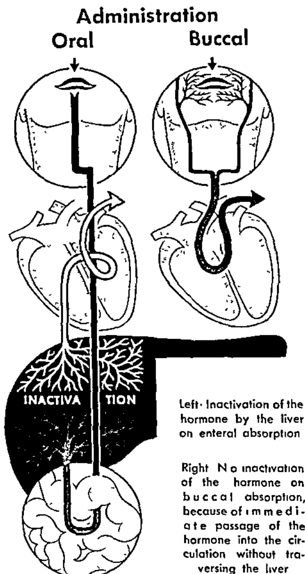
These various types of preparation for administration are available to the physician for hormone therapy. Hormones may be supplied to the body perorally, perbuccally, perlingually, transcutaneously, and even rectally; they may also be injected intramuscularly and sometimes intravenously, and implanted in pure form. Every mode of administration is associated with a different intensity and duration of hormone action, as well as a different rapidity of onset of action For this reason, uniform standardization, such as has been attempted for 25 years, is impossible. The many clinical conditions, which are now recognized as consequences of disturbances of equilibrium of the endocrine system and must therefore be treated with hormones, call for very different types of hormone effect as regards duration, intensity and onset of action The skilful physician can utilize the varied action of the different forms of administration to achieve the necessary *type of hormone effect, and thus adapt this therapy to the physiological* hormone requirements.

Peroral administration of hormones is convenient for physician and patient and has many advantages. However, only the preparations Progynon C, Progynon M, Proluton C, and Primodian develop their full endocrine effect on the usual oral administration, since they are not destroyed in the bowel, and are not inactivated by the liver when they reach the portal circulation. Tablets of Progynon C, and Progynon M, as well as Proluton C and Primodian, may therefore be swallowed, since their chemical properties protect them to a large extent from inactivation on passage through the liver [386, 387]. These tablets or dragees should be taken in divided doses throughout the day, during or after meals.

All other hormones from which a full effect is necessary after intake must not be swallowed, but must be allowed to disintegrate slowly in the mouth. They thence find entry into the organism by slow and continuous absorption via the mucosa over the *upper jaw and the cheek. If this is not done,* they would be partially destroyed in the gastro-intestinal tract, extensively inactivated in the liver, and thus rendered *ineffective to a* considerable degree ([388, 389]; see Fig. 39)

Buccal *administration of hormones has proved very valuable* [390]. In this form of administration a small tablet is inserted into the canine fossa between the upper lip and the gum (see Fig. 40) The drug remains at this site until it is dissolved, without causing discomfort. Since salivary secretion is not stimulated by this manoeuvre, the danger of swallowing quantities of hormone is practically absent. This form of administration is called "buccal" because the buccal mucosa is the principal site of absorption of the tablet. In the canine fossa, the drug is surrounded on all sides *by mucosa with a good blood supply, so that absorptive conditions* are there optimal.

With buccal administration, drugs *take the* same way as *with* injection treatment After absorption through the buccal mucosa. the hormone passes into the venous circulation immediately and thence via the heart and arteries into the tissues, without the possibility of inactivation by the liver—as may occur after swallowing on oral administration. Buccal administration is thus in effect parenteral administration. It is a special advantage of buccal administration that small amounts of hormone are continuously absorbed. In this way an even supply of active agent *is achieved, as occurs with the healthy endocrine gland* under physiological conditions. If a tablet is placed in the canine fossa before retiring, the supply of hormone continues without interruption throughout the night If absorption through the buccal mucosa is utilized, the quantities of hormone required for a certain therapeutic effect are scarcely any greater than with



Left· Inactivation of the hormone by the liver on enteral absorption

Right No inactivation of the hormone on buccal absorption, because of immediate passage of the hormone into the circulation without traversing the liver

Fig 39

intramuscular injections. Thus, experimental and clinical trials have shown [391, 392] that the dosage ratio between the amount of Primocort injected and the amount absorbed through the buccal mucosa to produce the same effect is about 1 : 1.5, a remarkably favourable ratio.

In summary, the following may be stated: Buccal administration renders possible division of the hormone dose required into several doses each day; this leads to an even supply of hormone, specially adapted to the needs of the organism. This continuous supply of small amounts of hormone closely resembles the physiological supply of hormone.



Fig 40

The following are now available for buccal use: Adrenal cortical hormone in the form of Primocort tablets containing 1 mg. desoxycorticosterone acetate, male sex hormone in the form of Testoviron tablets containing 2 mg. and 5 mg. methyltestosterone, as well as 25 mg methylandrostenediol tablets, and oestrogen as Progynon dragees containing 0 1 and 1 mg oestradiol. Administration of the dragees or tablets is distributed throughout the day, the tablets being introduced into the canine fossa about one-quarter hour after meals.

Another possible route for hormone administration is the p e r l i n g u a l one, solutions are readily absorbed through the lingual mucosa [393 394]. This type of administration is also far superior to absorption via the gastro-intestinal tract. Experience has

led to the introduction of oestradiol in alcoholic solution as Progynon drops.

Passage through the liver is also avoided in transcutaneous administration of testosterone as Testoviron T. The alcoholic drops are rubbed at regular intervals into the delicate skin of the bend of the elbow or the inner side of the thigh. Utilizing substances dissolved in oil for transcutaneous administration has not been so successful, since fat-free solvents penetrate the skin better. Progynon in ointment should also be mentioned in this connexion. With this type of administration in certain skin conditions the effect obtained is rather a cutaneous one than a transcutaneous one.

Intramuscular administration of hormones has proved very effective. This route is used when frequent supply of large doses of hormones is required, and a constantly repeated intensive effect is necessary. With this route the effect appears slowly and not suddenly. Hormones dissolved in oil, especially those esterified with benzoic, propionic or acetic acid, have an enhanced effect, which is also significantly prolonged. Exact standardization by units of weight permits accurate dosage at each administration, and therefore satisfactory control of the whole course of treatment. These short-term depot doses given at intervals enable therapy to approach physiological rhythm; in most cases – particularly in gynaecology, but also in severe deficiency syndromes after castration or in Addison's disease, etc. – such a rhythm is absolutely necessary and desirable.

Intravenous administration of hormones is only suitable in very special circumstances. Progesterone therapy in threatened or habitual abortion can be rendered very effective by giving the progesterone intravenously. Whereas in habitual abortion, for example, progesterone is injected intramuscularly as a prophylactic, the appearance of bleeding or uterine contractions may often be arrested immediately by giving the hormone intravenously [395]. Primolut intravenous is available for intravenous

administration of progesterone [396, 397, 398]. For intravenous *Cortiron therapy there is also a water-soluble* preparation in the form of desoxycorticosterone glucoside.

A convenient form of administration which is gaining in popularity is the use of hormone depot preparations with an action protracted over several weeks. Crystal suspensions have mostly been used so far, but they have the disadvantage that the extent of protraction depends considerably on the size of crystalline nucleus [399]. However, the size of the lumen of needles sets a limit on the use of large crystals. There are also certain objections in the case of women with an intact uterus to the repeated employment of depot preparations of oestrogen [400]. In sexually mature women, *depot therapy with oestrogens given without reference to the endocrine regulation of the menstrual cycle is unphysiological.*

Testoviron-Depot is particularly promising and economical; it is a clear fluid even in high concentrations (250 mg per c.c.). Since therapy with the male sex hormone must almost always be continued over a long period at an even rate there is an extraordinarily wide field of indications for Testoviron-Depot. With a single injection an effect is obtained for 2—4 or even at times 6 weeks; animal experiments have shown that quantitatively the effect is equal to that of several times the amount of testosterone in the usual form. This fact makes Testoviron-Depot a particularly economical preparation in disease conditions requiring high dosage for a prolonged period (carcinoma of the breast, post-castration signs).

Implants represent a further mode of administration of hormones; by means of these the pure hormone is implanted into the body tissues. Such an implant gives off a small but even supply of hormone for several months. It is therefore suitable for permanent substitution therapy with small doses over a particularly long time. In comparison with oily solutions of hormones, the onset of effect of implants is even more delayed. Absorption

from the depot usually takes several days to get going. Hence in conditions in which, in addition to a prolonged and continuous supply of hormone, a rapid onset of effect is desirable it may be convenient to give several supplementary intramuscular injections at the beginning.

At times a thick and non-vascularized capsule, the so-called "ghost formation" [401], forms around the implant. This is due to deposit of protein and formation of protein membranes on the surface of the implant. Such a capsule slows up and diminishes absorption from the implant, and may even arrest it altogether [402]. The speed of absorption depends on individual conditions in the organism, the site of implantation, and the consistency, surface area and size, i. e. the stereometric factors in the implant It has also been shown that individual hormones implanted in the same manner are absorbed at different rates [403, 401]. By means of implantation, the same effect can be obtained with smaller doses of hormone than are needed with intermittent injection treatment. The advantage of implantation is that physician and patient are independent of each other for quite long periods. The continuous supply of hormone to the body makes substitution therapy possible either permanently or for long periods. This is by no means always desired, and implantation of a hormone in such cases may even be a therapeutic error (e g in disturbances of menstruation; see page 129).

For introduction of sterile implants, the region of the posterior axillary line, one of the lower abdominal quadrants, or in women the lower fold of the breast (or even in rare cases the labia majora) may be chosen. Very recently, experiments have been made with direct implantation of testosterone into the testes [118, 405, 406]

Best results as regards healing are probably obtained by implanting under the fascia (subfascially) A small incision is made into the skin, a subfascial pocket is fashioned in the musculature

administration of progesterone [396, 397, 398]. For intravenous Cortiron therapy there is also a water-soluble *preparation in the* form of desoxycorticosterone glucoside.

A convenient form of administration which is gaining in popularity is the use of h o r m o n e d e p o t p r e p a r a t i o n s with an action protracted over several weeks. Crystal suspensions have *mostly been used so far, but they have the disadvantage that the* extent of protraction depends considerably on the size of crystalline nucleus [399]. However, the size of the lumen of needles sets a limit on the use of large crystals. There are also certain objections in the case of women with an intact uterus to the re*peated employment of depot preparations of oestrogen* [400]. *In* s e x u a l l y m a t u r e w o m e n, depot therapy with oestrogens given without reference to the endocrine regulation of the menstrual cycle is unphysiological.

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tion Both preparations show only very slight protein reactions, so that transient signs of anaphylaxis are only seldom observed.

The frequently disputed question whether oestrogens can be used as abortifacients must be categorically denied both on theoretical grounds and on the basis of many years of animal experiment and clinical experience (407, 408, 409, 410, 411, 412). Occasional reports of successful employment of the follicular hormone for interruption of pregnancy are explicable on the basis of incorrect diagnosis. An important factor in these observations is also the common occurrence of non-viable embryos. Indeed, a modern form of therapy in threatened and also habitual abortion actually consists of continued administration of very large amounts of oestrogen (413, 414, 415, 416) (see page 155).

Summary of principles of treatment

The principles of treatment are derived from the physiological and pharmocological effects of hormones. Dysfunctions of endocrine glands can be overcome successfully by supply of hormones provided that the diencephalon, pituitary and effector organs are still capable of reaction and function. For example, the prerequisite for successful use of progesterone to regulate the menstrual cycle is a certain degree of proliferation of the endometrium. A permanent result in the treatment of cystic glandular hyperplasia with corpus luteum hormone is possible only if the disturbed interplay between ovary, pituitary and diencephalon can be brought back on to the right lines. For this, however, it is essential that all these organs should be still capable of responding and functioning Administration of female sex hormones to sexually mature women must always be timed properly in relation to the menstrual cycle and physiological rhythm. Exceptions to this rule are described under the individual indications. Supply of hormones must be individually adapted to the organism, and usually in physiological dose ranges. The ther-

by blunt dissection, haemostasis is carefully carried out, and the implant is let fall into the pocket by spreading out a special holder and then pushed home. The incision is closed by a suture or clip. Excessive physical movement should be avoided at first in order to facilitate healing in of the implant. Occasionally the implant is extruded though sterile. Every implantation must be carried out under strict aseptic precautions. Extrusion of the implant with suppuration is the consequence of a procedure not carried out aseptically or according to instructions.

What form of hormone administration is chosen in any case depends on the requirements for successful therapy as regards onset of action, and intensity and duration of hormone effect.

Since hormones occur naturally in the body, tolerance to them is usually good. In the dosages recommended for therapeutic purposes, side-effects and damage to organs need not be feared. Hormone treatment which is carried out for too long, or in incorrect dosage, or for the wrong indications may however lead to damage. If any special signs of intolerance appear, the question should always be raised whether the dosage is not too high or whether the hormone under administration is not actually contraindicated. The best known example of this is the clinical picture of hyperfolliculinism (hyperoestrinism) mentioned on page 84. In every case therapy must be adapted to the sex, the organism, and the age of patient; dosage must take into account the clinical picture and the results desired. With intelligent therapeutic techniques based on experience, physiological conditions may be restored with hormones, provided that the indication is correct Where the indication is to save life, as in prostatic carcinoma, the appearance of signs of overdosage must be taken into account.

The gonadotropins, Priantin and Primogonyl, are glucoproteids, and can therefore be injected in solution in physiological saline — preferably intramuscularly The contents of an ampoule of these preparations should be employed immediately after solu-

Hormone Preparations of the Schering A.G. Berlin

(Forms of Packing)

Progynon dragees

Oestradiol

For buccal employment

Dragees, each of 0.1 mg. = 1,000 i. u.

Dragees (forte), each of 1 mg. = 10,000 i. u.

Progynon implants

Oestradiol

For implantation

Implant of 10 mg

Implant of 20 mg

Progynon B oleosum

Oestradiol benzoate

For intramuscular injection

Ampoules of 1 c.c. = 1 mg

Ampoules (forte) of 1 c.c. = 5 mg.

Progynon ointment

Oestradiol

For transcutaneous use

Tubes containing about 20 g. (1 g. contains 0.1 mg. oestradiol)

8*

apeutic dose of hormone may vary widely according to the situation. Large doses do not enhance the therapeutically desired effect; they may even produce the opposite effect.

Therapy with the hormone of the opposite sex is indicated only in certain disorders, and demands particularly accurate dosage (see pages 159 and 174).

Hormone Preparations of the Schering A.G. Berlin

(Forms of Packing)

Progynon dragees

Oestradiol

For buccal employment

Dragees, each of 0 1 mg = 1,000 i. u.

Dragees (forte), each of 1 mg. = 10,000 i. u.

Progynon implants

Oestradiol

For implantation

Implant of 10 mg

Implant of 20 mg.

Progynon B oleosum

Oestradiol benzoate

For intramuscular injection

Ampoules of 1 c c. = 1 mg.

Ampoules (forte) of 1 c.c. = 5 mg.

Progynon ointment

Oestradiol

For transcutaneous use

Tubes containing about 20 g (1 g. contains 0.1 mg oestradiol)

Progynon drops

Oestradiol in alcoholic solution

For perlingual use

Drop bottles containing 10 c.c. = 2 mg.

Progynon C

Ethinyl oestradiol

For oral employment

Tablets, each of 0.02 mg.

Progynon M

Ethinyl oestradiol

For oral employment

Tablets, each of 0.2 mg.

Proluton C

Pregneninolone

For oral employment

Dragees, each of 5 mg.
Dragees, each of 10 mg.
Dragees, each of 25 mg.

Proluton

Progesterone

For intramuscular injection

Ampoules of 1 c.c. = 5 mg.
Ampoules of 1 c.c. = 10 mg.
Ampoules of 1 c.c. = 25 mg.

Proluton implants

Progesterone

For implantation

Implants of 100 mg

Proluton intravenous

Progesterone in aqueous solvent agent

For intravenous injection

Ampoules of 1 c c. = 20 mg.

Duogynon

Progesterone plus oestradiol benzoate

For intramuscular injection

Ampoules of 1 c c. =

20 mg progesterone plus

2 mg. oestradiol benzoate

Testoviron

Testosterone propionate

For intramuscular injection

Ampoules of 1 c.c. = 10 mg.

Ampoules of 1 c c = 25 mg.

Ampoules of 1 c.c = 50 mg.

Testoviron implants

Testosterone

For implantation

Implants of 100 mg.

Testoviron-Depot

Testosterone as oenanthate and propionate

For intramuscular injection

Ampoules of 1 c.c. = 50 mg.

Ampoules of 1 c c. = 100 mg.

Testoviron-Depot

Testosterone oenanthate

For intramuscular injection

Ampoules of 1 c.c = 250 mg.

Testoviron T

Testosterone in alcoholic solution

For transcutaneous employment

Drop bottles containing 10 c c. = 30 mg

Testoviron tablets

Methyl testosterone

For buccal employment

Tablets, each of 5 mg.
Tablets, each of 10 mg.
Tablets, each of 25 mg.

Primodian tablets

Methyl testosterone plus ethinyl oestradiol

For oral use

Tablets, each containing 4 mg. methyl testosterone plus 0.002 mg. ethinyl oestradiol

Testoluton

Testosterone propionate plus progesterone

For intramuscular injection

Ampoules of 1 c.c. =
15 mg. testosterone propionate plus
10 mg. progesterone

Ampoules (forte) of 1 c.c. =
25 mg. testosterone propionate plus
10 mg progesterone

Methylandrostenediol "Schering A. G. Berlin"

Methylandrostenediol

For intramuscular injection

Bottles of 10 c.c. = 500 mg. as crystalline suspension

For buccal employment

Tablets, each of 25 mg.

Primocort

Desoxycorticosterone acetate

For intramuscular injection

Ampoules of 1 c.c. = 5 mg.
Ampoules of 1 c.c. = 10 mg.

Primocort implants

Desoxycorticosterone acetate — *For implantation*

Implants of 100 mg.

Primocort tablets

Desoxycorticosterone acetate — *For buccal employment*

Tablets, each of 1 mg.

Primocort intravenous

Desoxycorticosterone glucoside — *For intravenous injection*

Ampoules of 1 c.c. = 5 mg.
Ampoules of 5 c.c. = 50 mg.

ACTH "Schering A. G. Berlin"

Adrenocorticotropic hormone of the anterior pituitary

For intramuscular injection

Ampoules of 10 i. u.
Ampoules of 2.5 i. u.

Primothyron

Thyrotropic hormone of the anterior pituitary

For intramuscular injection

Ampoules of 500 guinea-pig units plus solvent

Priantin

Serum gonadotropin — *For intramuscular injection*

Ampoules of 1,000 i. u. plus solvent
Ampoules of 5,000 i. u plus solvent

Primogonyl

Chorionic gonadotropin — *For intramuscular injection*

Ampoules of 300 i. u plus solvent
Ampoules of 1,000 i u plus solvent

Therapeutic Use of Sex Hormones

The physician who seeks to employ the hormones described in this book therapeutically must have a knowledge of their site of formation, physiological functions which they fulfil in the organism, and (last but not least) their pharmacological properties. The indications, guidelines, and possibilities in hormone treatment are derived from scientific knowledge and clinical experience. Success can be expected only in so far as the causal *relationships have been correctly assessed, and the nature of the* functional disturbance exactly analysed. Furthermore, the mode of administration and the dosage must be carefully chosen, since each patient requires individual treatment. Like other drugs, hormones are no "miracle drugs." As elsewhere in therapy, the physician must use all his skill in order to obtain the optimum effect from hormones, and really exhaust their therapeutic possibilities.

Therapeutic Use of Sex Hormones in Women

Amenorrhoea

The cause of amenorrhoea may be a local one. the absence of a period is then the result of malformations or an underdevelopment of the genitals, even to the extent of infantilism (hypoplasia of the genitalia and disturbance of total development). Even so, there remains a not inconsiderable number of cases in which, in spite of normal uterine development and normal secondary sex characters, periodic bleeding is absent and the endocrine stimulus to the first or to later ovulations is lacking. In every case of amenorrhoea a detailed examination is necessary. The question must be clarified whether, besides constitutional aberrations or deficiencies which might also be related to an ovarian insufficiency, other causes can be held responsible for the absence of menstrual bleeding. Investigation will by no means always reveal gross anatomical changes. Even mild physiological disturbances may be the cause of anomalies of menstrual cycles (functional amenorrhoea) or of their first absence.

Primary amenorrhoea means that, although a woman has reached the correct age, no spontaneous menstrual bleeding has yet appeared.

Secondary amenorrhoeas, on the other hand, are those in which the menstrual period has been absent for a shorter or longer time, and for various causes, after the regular appearance of menstruation, usually over a long period.

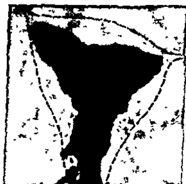
Primary amenorrhoea

Hormone treatment of primary amenorrhoea requires a particularly conscientious and careful assessment of indications. The

prospect of cure must be evaluated with reserve, since a p e r m a n e n t r e s u l t beyond the period of hormone treatment cannot always be anticipated. It is true that it is usually possible *by rhythmical administration of hormones to produce bleedings* resembling menstruation, but it is rare to achieve ovulation.



Hypoplastic human uterus



The same after 5 injections of oestradiol benzoate

Development of a hypoplastic uterus with oestrogen treatment (after CLAUBERG)

Fig 41

Primary amenorrhoea has its principal cause in a constitutionally determined underdevelopment, the most marked type being *found in the clinical picture of infantilism* The disturbance of total development is usually accompanied by underdevelopment of the ovaries and uterus. It is however not uncommon to find ovaries of normal size with a disturbance of follicle matura-

tion. Conversely, a hypoplastic uterus can coexist with a normal body build and secondary sex characters. A disturbance in the controlling centres is frequently recognized as the real cause [417].

Therapeutic measures depend on the clinical findings. If there is considerable disturbance of development associated with a constitutional deficiency, general measures designed to promote and strengthen development are at least as important as endocrine treatment. The latter is more likely to succeed if, apart from the uterine and ovarian growth to normal produced by hormones, a concomitant constitutional improvement can be attained by general tonic measures. Treatment can be carried out either with oestrogens or with gonadotropic hormone or with both. To a great extent, the results of treatment depend on the age of the patient. Women under the age of 20 offer the best prospects of cure; women over this age seldom obtain permanent cures [418, 419, 420]. Treatment must continue for a long time. In the case of women *with a hypoplastic uterus, it consists of regular* injection of 5 mg. Progynon B oleosum forte intramuscularly every 4 days for 5 doses, the course being continued for 3 to 6 months. After a 20-day course of injections has been finished, an interval of about a week is interpolated before continuing oestrogen treatment as above. Supplementary progesterone medication may at first be omitted. Only when the uterus has developed to approximately normal size (see Fig. 41) should the series of Progynon B oleosum be followed by 5 injections on successive days of 5—10 mg. Proluton intramuscularly. Bleeding then usually begins after a few days. This was the procedure by which Kaufmann first in 1933 induced in a castrated woman a proliferative change in the endometrium (see Fig. 42), then secretory transformation (see Fig. 43), and finally menstruation (Kaufmann's proliferative dose, Kaufmann's complete course) [83]. Treatment of primary amenorrhoea with normally developed genitalia can be carried out from the start with cyclical rhythm, i. e. with oestrogen and progesterone. Five in-

jections, each of 5 mg. Progynon B oleosum forte, are given over 20 days, and followed from the 21st to the 25th day by daily injection of 5—10 mg. Proluton or more intramuscularly.



Endometrium in the proliferative phase after administration of 25 mg. oestradiol benzoate to a castrated woman

Fig. 42

For treatment of primary amenorrhoea, employment of implants has recently been recommended, as also in other indications which will be discussed later (see page 225). This technique certainly offers the advantage of saving hormone (see page 110) and of a prolonged and even supply of hormone to the body. It is however a disadvantage of this continued supply of hormone that it may lead, if the uterus is still present, to proliferative changes in the endometrium, known under the name of cystic glandular

hyperplasia [84]. The employment of implants therefore appears to be justified in principle only if it is desired to furnish a continuous supply when the uterus is absent or underdeveloped This latter condition relates to primary amenorrhoea in its early



Endometrium in the secretory phase after treatment of a castrated patient with 25 mg oestradiol benzoate and 25 mg progesterone

Fig 43

stage, when the object is to promote the development of the uterus. Implantation of 20 mg Progynon is sufficient for adequate promotion of uterine growth over a period of about 2 to 4 months [84]

If the implant leads to hyperplastic bleeding, it is necessary to inject daily 10 mg. Proluton or 25 mg Testoviron intramuscularly until bleeding ceases. In special cases it may even be necessary to remove the implant.

Implantation treatment of primary amenorrhoea should be practised only by physicians with extensive experience of the hormone treatment of this deficiency state. Recent experience has shown that the anterior pituitary gonadotropins which control the function of the gonads are also suitable for the treatment of primary amenorrhoea. The use of Priantin, which contains in the first place follicle-stimulating factor, is particularly promising (see Suggestions for Dosage, page 225).

Secondary amenorrhoea

The treatment of secondary amenorrhoea is more promising than that of primary amenorrhoea. Two forms can be distinguished clinically. the amenorrhoea of l e s s than one year's duration, and the amenorrhoea of m o r e than that duration.

The cause of the absence of menstruation may lie in a general hypofunction of the genitalia, or in the ovaries, pituitary or thyroid. The condition may also be due to intoxications (poisons, nicotine, infectious diseases, etc.), environmental influences, mental and physical stress (functional amenorrhoea), malnutrition, isolation, pregnancy, lactation, anaemias of various origin, morbid anatomical changes, and so on. The prospect of a successful outcome of hormone treatment is in direct relation to the degree to which the amenorrhoea is caused by lack of sex hormones. or deficient or aberrant function of other endocrine glands The duration of amenorrhoea is of great significance for the prognosis. The shorter the period of amenorrhoea and the younger the patient, the more likely is treatment to be successful In principle, with few exceptions, every case of amenorrhoea lasting for more than two months should be submitted to treatment. In these cases of amenorrhoea of short duration, success is obtainable in a high percentage. Specially good and rapid results are obtained with Duogynon [121] (see pages 128 and 225) This preparation can also be used as a pregnancy test, the result

then being negative. The orally effective Progynon C, of which 1.7—2.5 mg. suffices to build up a proliferative phase, has been successfully used in secondary amenorrhoea.

If bleeding is absent for a prolonged period, it may be expected that there will be atrophy of the internal genital organs, especially the endometrium. For this reason, the proportion of therapeutic successes falls with a duration of amenorrhoea of over one year from 40 to 25%; according to some authors the proportion is even less [422]. Every patient should be induced to keep a careful menstruation calendar. In amenorrhoeas not of endocrine origin, the other possible causes must be sought, and treatment should correspond to that of primary amenorrhoea (see Suggestions for Dosage, page 225).

Uterine hypoplasia (hypohormonal amenorrhoea)

If the cause of the amenorrhoea is a uterine hypoplasia (often associated with acute-angled anteflexion and retroposition), it may be assumed that oestrogen production is too little. The appearance of menstrual periods may then be expected after 2 to 3 months of treatment with 1 mg. Progynon B oleosum, or in severe cases 5 mg Progynon B oleosum forte (5 mg every 4th day for 20 days up to a total dose of 25 mg.) If this method of treatment is unsuccessful, a trial should be made of the Kaufmann schedule mentioned on page 123, with associated Proluton treatment. It should however be noted that a uterine hypoplasia may also be present with a normal menstrual cycle.

After the first menstrual period has appeared, the artificial supply of oestrogen and progesterone may be still necessary over a prolonged period, in order to build up a natural, spontaneous rhythm. In such cases, correct cyclical timing in the administration of the two hormones is an obvious requirement The use of implants may be considered at the beginning of treatment.

Hyperhormonal amenorrhoea

The diagnosis of this not uncommon clinical picture can be el cidated by the demonstration of an unphysiologically high oestro *gen excretion, or by the recently employed demonstration o* oestrogen reactions in the vaginal epithelium [423, 424, 425, 426, 42 428, 429, 430, 431]. Endometrial biopsy is a simpler diagnostic aid *the endometrium being found in a state of great proliferatio* [432, 433]. Treatment with 40—60 mg. Proluton (10 mg. daily intra muscularly) induces bleeding. Reliable results are also obtaine with Duogynon, *which should be tried first in every case.*

Withdrawal bleeding

The bleeding which appears after treatment with l a r g e *doses* of oestrogen is not always a true menstrual period, with a previous secretory phase in the endometrium. After administration of large doses of oestrogen there is first a proliferation, then a disintegration of the proliferated endometrium and a so-called withdrawal bleeding. This phenomenon also shows the need to administer oestrogen and corpus luteum hormone in physiological rhythm, in order to produce regular proliferation in the endometrium and then transformation of the latter into the secretory phase (see also the next section)

Brief treatment of secondary amenorrhoea

It has been observed that brief combined treatment with progesterone and oestrogen (Duogynon = *20 mg. progesterone plus 2 mg. oestradiol benzoate per ampoule) leads to bleeding* in amenorrhoea of short duration (amenorrhoeas of psychical origin, women with *labile cycles)* [388 434, 435 421 713]. *It is evident that most of* these bleedings are due to diapedesis. A single intensive dose of hormones has the advantage of being effective also *in hyperhormonal* amenorrhoea (see above), and can thus be recommended in any case of secondary amenorrhoea which has not been present for too long.

This therapeutic technique does not cause the appearance of bleeding from the pregnant uterus. This fact shows the significance of Duogynon as a p r e g n a n c y t e s t in practice. If Duogynon is injected on two successive days and no bleeding appears during the succeeding 2—6 days, pregnancy can be diagnosed with a high degree of probability [436, 437]. The need for confirmation of the diagnosis by other methods of examination is obvious.

Corpus luteum persistence

Apart from the pathological picture of cystic glandular hyperplasia, caused by persistence of the follicle and consequent increase in oestrogen formation, another type of excessive hormone formation by the ovary is known; this is the picture of so-called corpus luteum persistence. The unusual amount of progesterone formed leads to a delay in the menstrual period and to the formation of an extraordinarily tall endometrium with the changes of the secretory phase The inhibition of gonadotropin output by the anterior pituitary caused by large doses of oestrogen leads to restoration of the cycle to normal (see page 30).

Finally it should be stressed that the diagnostic difficulties involved in the origin of amenorrhoea may be considerable. Moreover, it should be clearly understood that not every case of amenorrhoea requires immediate hormone treatment. Occasionally, as in severe infections such as tuberculosis, the amenorrhoea is the expression of a protective mechanism on the part of the organism (so-called protective amenorrhoea). In these cases treatment with sex hormones should be avoided

Disturbances of menstruation

Hormone treatment of disturbances of menstruation is of wide scope in practice. Such disturbances are principally distinguished by changes in tempo of bleeding, amount of bleeding and duration of bleeding, but also differ from normal menstruation as

regards behaviour of basal temperature and reaction of the vagina (see Figs. 44—46 and 48). The causes and clinical pictures of these disturbances vary greatly.

Schema of Menstruation

	1st—4th day	5th—10th day	11th—15th day	16th—28th day
Menstrual Cycle	Menstruation: Duration: 4 days	Intermenstruum—Duration 24 days		
		Proliferation phase Duration 11 days		Secretory phase Duration *13 days* or Premenstruum or Pregravid phase
	With casting off and bleeding } Desquamation	*Postmenstruum* Duration: 6 days	*Interval* Duration 5 days	
	With healing } Regeneration	Beginning of growth in thickness	Completion of growth in thickness	
Ovarian Cycle	Cessation of corpus luteum hormone and regression of corpus luteum due to death of ovum	Beginning maturation of a new follicle	Complete maturation of new follicle	Follicle rupture on the 14th 16th day Formation and stage of maturation of corpus luteum

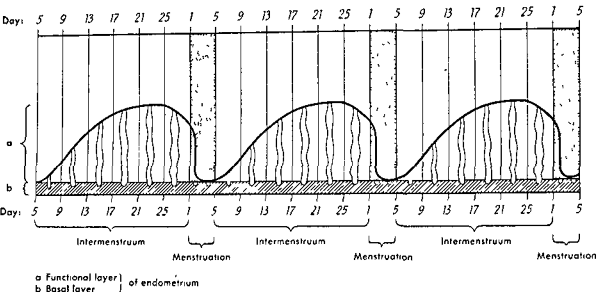
Schema of menstruation (after Boenig [illegible])

Fig 44

With a knowledge of endocrine functions, however, the employment *of female sex hormones is relatively simple.* It should never be forgotten that atypical bleeding is in the long run simply a symptom of a disturbance of a functional process. It is often impossible to recognize the cause of the disturbance from the type of bleeding alone It is therefore highly advisable, in addition to a diagnostic curettage, to have the morning temperature taken, since the latter provides a simple means of estimating the duration of the proliferative and the secretory phases [473]

Hypomenorrhoea

Hypomenorrhoea, which is characterized by regular but scanty bleeding, responds poorly to hormone treatment [438]. According to some authors, the cause lies in an increase in vascular con-



Schematic representation of normal menstruation

Fig. 45

regards behaviour of basal temperature and reaction of the vagina (see Figs. 44—46 and 48). The causes and clinical pictures of these disturbances vary greatly.

Schema of Menstruation

	1st—4th day	5th—10th day	11th—15th day	16th—28th day
Menstrual Cycle	Menstruation: Duration: 4 days	Intermenstruum—Duration 24 days		
		Proliferation phase Duration, 11 days		Secretory phase Duration 13 days or Premenstruum or Pregravid phase
	With casting off and bleeding } Desquamation	Postmenstruum Duration, 6 days	Interval Duration, 5 days	
	With healing } Regeneration	Beginning of growth in thickness	Completion of growth in thickness	
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Schema of menstruation (after Boenig [168])

Fig 44

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Hyper- and Polymenorrhoea

1 - 28	1 - 28	1 - 28	1 - 28	1 - 28

Hypo- and Oligomenorrhoea

1 - 28	1 - 28	1 - 28	1 - 28	1 - 28

Metrorrhagia

1 - 28	1 - 28	1 - 28	1 - 28	1 - 28

Menorrhagia

1 - 28	1 - 28	1 - 28	1 - 28	1 - 28

The various types of endometrial bleeding
(continued)

Fig 46b

Eumenorrhoea	1 - 28	1 - 28	1 - 28	1 - 28	1 - 28
Amenorrhoea	1 - 28	1 - 28	1 - 28	1 - 28	1 - 28
Hypermenorrhoea	1 - 28	1 - 28	1 - 28	1 - 28	1 - 28
Polymenorrhoea	1 - 28	1 - 28	1 - 28	1 - 28	1 - 28

The various types of endometrial bleeding
(Modified from diagrams by Martius)

Fig. 46a

ances (e. g. with environmental change) or poor contractility of the uterus, or in some cases an excess of oestrogens as a result of persistence (often repeated) of the follicle. Among this multiplicity of causes the true origin must be elucidated before treatment begins. If progesterone formation is inadequate, or the secretory phase shortened, progesterone alone is indicated. Therapy may be begun in the first half of the cycle with oestrogens, and continue in the second half with corpus luteum hormone, and in case of an excess of oestrogens be successfully carried out with testosterone (see also page 160). The combination of testosterone and progesterone (Testoluton) is particularly effective.

Polymenorrhoea

As a rule a regular 28-day cycle is considered normal Many authors have, however, pointed out that deviations from this cycle both above and below this figure may still be within the range of normal (see also page 33). Nevertheless there are pathologically shortened cycles of three weeks and less, whose cause lies in a shortened span of corpus luteum function and whose treatment may consist in administration of progesterone or better still, Duogynon It is therefore advisable to determine by basal temperature recording whether the proliferative or the secretory phase is shortened (see also page 147). Pathologically shortened cycles of this nature are specially found at the beginning and end of sexual maturity, under adverse influences of the environment, and as a concomitant of infectious diseases.

If the proliferative phase is shortened, treatment with corpus luteum hormone is not successful (cf. page 148). In these cases advantage should be taken of the inhibiting influence of oestrogens on the folliculotropic factor of the anterior pituitary, by giving between the 4th and 6th days of the cycle one or two intramuscular doses of 5—10 mg. Progynon B oleosum forte ("Displacement effect") [443, 444, 445].

traction and a rise in capillary resistance of the blood vessels of the uterus. These patients are usually vasolabile, with a sensitive autonomic nervous system, and tend to have violent contractions of the vessels in the stratum basalis. Other authors have observed in some cases of hypomenorrhoea that the cyclical changes in the endometrium follow an abnormal course. They would interpret the small extent of the bleeding and the slow reconstruction of the mucosa as consequences of a delay in the fall of level of corpus luteum hormone. A therapeutic trial can be made with Progynon in the first half of the cycle and Proluton in the second half [139, 140] (see also page 246).

Oligomenorrhoea

Oligomenorrhoea may be due to a subliminal cycle or to delayed maturation of the follicle. Sometimes several consecutive subliminal cycles, in which a mature follicle disintegrates prematurely, simulate the picture of amenorrhoea. If the internal genitalia are underdeveloped in such cases, correctly timed administration of oestrogens has proved of value. If the internal sex organs are of normal size, however, success will be obtained with progesterone, of which 5—10 mg. intramuscularly should be given 2 to 5 times during the ten days before the period is expected.
A further possibility for treatment consists in the injection of 5—10 mg. Progynon B oleosum intramuscularly in the first half of the cycle, and a total dose of 10—20 mg of Proluton intramuscularly in the second half. Particularly good results are obtained if 5 mg., or in case of failure 10 mg., of Progynon is injected on the 21st day, followed by 10 mg, or in case of failure 20 mg., of Proluton on the 23rd day of the cycle. A period then usually appears on the 26th to 28th day [141, 142].

Hypermenorrhoea

Hypermenorrhoea is often due to organic changes, such as chronic inflammation of fibroids Other causes are functional disturb-

ances (e. g. with environmental change) or poor contractility of the uterus, or in some cases an excess of oestrogens as a result of persistence (often repeated) of the follicle. Among this multiplicity of causes the true origin must be elucidated before treatment begins. If progesterone formation is inadequate, or the secretory phase shortened, progesterone alone is indicated. Therapy may be begun in the first half of the cycle with oestrogens, and continue in the second half with corpus luteum hormone, and in case of an excess of oestrogens be successfully carried out with testosterone (see also page 160). The combination of testosterone and progesterone (Testoluton) is particularly effective.

Polymenorrhoea

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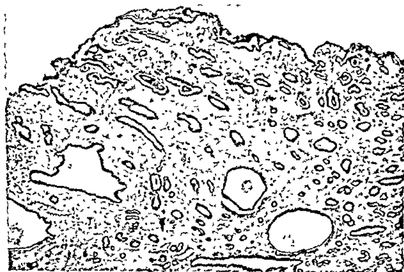
Menstruation can also be delayed by several days by giving testosterone; this effect takes place via the anterior pituitary as with oestrogens [416]. Significantly larger doses are necessary for this purpose; a total of 200 mg. should be injected shortly after the conclusion of a menstrual period, as above. This measure is utilized, for example, for actresses, sportswomen and dancers, who need a temporary delay in menstruation for professional reasons [447, 448].

Metropathia haemorrhagica cystica (menorrhagia)

Bleeding is too frequent and too prolonged in metropathia haemorrhagica cystica (cystic glandular hyperplasia). The severe haemorrhages which occur in this condition are so irregular that a cycle is no longer recognizable. This condition is particularly commonly observed in women after the age of 40. The cause is supposed to be a disturbance in the regulating mechanism in the diencephalon and the anterior pituitary. The continued inflow of oestrogens due to persistence of the follicle, the inhibition of output of luteinizing gonadotropin from the anterior pituitary, and the lack of corpus luteum hormone lead to excessive proliferation of the endometrium ([422, 419, etc]; cf. Fig. 47). There is thus a hyperoestrinism, at least for a time Diagnosis of this disorder must be confirmed by curettage, which is needed to exclude malignant tumour

During the epoch of sexual maturity, therapy with corpus luteum hormone offers good prospects of success, provided the dose is high enough. The haemorrhages cease as a result of the transformation of the endometrium into the secretory phase, and the casting off of the latter by normal menstruation. At least 5—10 mg. Proluton should be given intramuscularly every day for 6 days, and in severe cases even more. Treatment may begin by injection intravenously of 1 or 2 ampoules of Proluton (20 to 40 mg.) [450]. Since recurrence of the haemorrhage is not uncommon, it is advisable to continue prophylactic Proluton treatment

for several months during the period between the 19th and 24th days of the cycle. Cystic glandular hyperplasia can also be treated with Progynon. Especially if bleeding has continued for a fairly long time and the endometrium has desquamated, oestrogens will produce temporary haemostasis [151]. The effect is due



Endometrium in cystic glandular hyperplasia
Fig 47

to removal of the oestrogen deficit which has occurred [152], *and* perhaps also to the output of luteinizing hormone from the anterior pituitary In resistant cases, the administration of gonadotropic hormone in the form of Primogonyl may be indicated for its luteinizing action, to ensure a permanent effect by an indirect influence on the metropathic bleeding (cf page 203).

Testosterone may render oestrogens ineffective to a certain extent, and perhaps even cause regression of the persistent follicle. The male sex hormone also produces an anaemia of the endo-

Oestrogenic phase	
a) no maturation of the follicle:	Amenorrhoea with a resting endometrium.
b) poor maturation of the follicle:	Prolonged menstrual bleeding as a result of defective regeneration, frequently in association with prolonged menstrual desquamation
c) slow follicle maturation:	Oligomenorrhoea with a two-phase cycle.
d) brief persistence of the follicle:	Approximately rhythmical bleedings from a hyperplastic uterine mucosa.
e) prolonged persistence of the follicle:	After amenorrhoea, irregular bleeding from a hyperplastic endometrium.

Differentiation of uterine haemorrhage by means of the histological picture of the endometrium
(After von Mossenbach [736])
Fig 48a

metrium As a result, bleedings cease. For at least 4 consecutive days, 25—50 mg. Testoviron should be given daily by intramuscular injection. In the light of clinical experience so far, it is impossible to give a definite opinion on the mode of action of this type of therapy [422] Combined treatment with progesterone and testosterone can also be highly recommended [153]. Bleeding is usually arrested by giving 10 mg. Proluton and 25 mg. Testoviron (as present in Testoluton forte), provided that therapy is begun early enough, i. e. before desquamation of the endometrium.

Corpus luteum phase	
a) no formation of corpus luteum:	Anovular cycles. Bleeding from proliferated mucosa at shortened intervals.
b) corpus luteum insufficiency:	Shortened intervals, with defective endometrial function
c) brief persistence of corpus luteum	Prolonged intervals, with prolonged bleeding (prolonged menstrual desquamation).
d) prolonged persistence of corpus luteum.	Amenorrhoea at first; later bleeding from a hypertrophic mucosa.

Differentiation of uterine haemorrhage by means of the histological picture of the endometrium

(Continuation)

Fig 48b

Therapeutically unjustifiable administration of large doses of oestrogens in other conditions may lead as a side-effect to an artificially induced cystic glandular hyperplasia Treatment of such artificially induced hyperplasias should be carried out according to the principles stated above, with immediate withdrawal of the oestrogen.

Dysmenorrhoea

Dysmenorrhoea often causes diagnostic and therapeutic difficulties because of the variety of its determinants. The clinical

picture may be due to changes in organs or in position, or to psychical or nervous factors. In older patients with a history of previously normal menstruation, the possibility of organic disturbances *(polyps, fibroids, etc.) should be specially borne in* mind.

The uterus is commonly found to be rigid, and in a continuous state of "spastic irritability." Thyroid hypofunction may also be an occasional cause of the symptom. If the uterus is hypoplastic, dysmenorrhoea is often associated with an oligomenorrhoea. The severe repercussions on the general condition of the patients, who may complain among other things of severe tension in the lower back and of downward pressure, make treatment necessary.

If a hypogenitalism is present, with acute-angled anteflexion and a conical, small portio vaginalis and long cervix, it is advisable to give in the first 14 days of the cycle 3 to 5 injections of 1 mg. Progynon B oleosum intramuscularly, or to prescribe Progynon dragees "forte" (buccally) [154]. It is necessary to repeat treatment over several cycles.

If uterine development is *normal*, dysmenorrhoea as well as other symptoms may be a sign of a transient hyperoestrinism or progesterone deficit. In these cases Testoluton is successful. One ampoule of 15 mg testosterone propionate plus 10 mg. progesterone is given intramuscularly on each of three days before menstruation, or shortly before pain is expected Treatment with corpus luteum hormone has also been recommended. On each of 5 successive days before the period, 5 mg. of Proluton is given intramuscularly [155]; in milder cases, up to 2 dragees each of 5 mg. Proluton C are given 3 times a day for 8 days previously. Even in these cases, treatment must be continued over several months. It is also obviously necessary to deal with any organic disorders present (cf page 160). American authors have had good results from the employment of Testoviron in many cases, giving 10—25 mg. intramuscularly 3 times a week for 1 week before the menses and during the menses [156].

Alternatively, one 5 mg. tablet of Testoviron can be given buccally 2—4 times a day. Pre-ovulatory treatment with testosterone may also be considered in older women, provided that no children are desired. Combined treatment with progesterone and testosterone, i. e. with Testoluton, in the premenstrual phase overcomes dysmenorrhoea when the latter is combined with breast pain, nervous changes, water retention, etc., i. e. symptoms of hyperoestrinism.

Mastodynia (premenstrual breast pain)

Women frequently complain of painful swelling of the breasts at about the middle of the intermenstruum, or even a few days before menstruation (premenstrual mastalgia). These symptoms appearing before the period are presumably due to a relative hyperoestrinism (457 458). Testoviron is particularly effective for these cyclical swellings, which are usually not associated with organic changes. Apart from injection treatment, local treatment by inunction of Testoviron T into the skin of the breast should be considered (459 460). Testoluton is particularly effective (cf. section on dysmenorrhoea)

Ovulatory bleeding

A clinical picture which has not yet been completely clarified is that of ovulatory bleeding. Whereas some persons are of the opinion that bleeding appearing at the time of rupture of the follicle is due to an excessively high level of oestrogens, others believe that the bleeding is an expression of the beginning of a fall in oestrogen level at the time of rupture (461, 462, 463). The various methods of treatment recommended are explained by this divergence of opinion. For this reason, small doses of Proluton (5 mg.) may be given daily from the 4th day on until the time at which bleeding is expected, or 5 mg. Progynon B oleosum may be given intramuscularly once or twice on the 13th—14th day of the cycle

Inflammatory disorders of the female genitalia:

Endometritis, especially after delivery or abortion

Pathogenic microorganisms of all types may penetrate into the uterine wall, penetration being favoured during the periods by the presence of polyps, submucous fibroids, and other factors; this not uncommonly leads to disturbances of menstruation and additional bleeding. Endometritis is particularly liable to happen after curettage, abortion or delivery. Defective regeneration of the endometrium in its healing phase, or small fragments of placenta, pave the way for pathogens and may lead to severe chronic inflammation with bleeding. If there is an oestrogen deficiency the endometrium appears to have a special tendency to inflammation and haemorrhage [74]. The fact that oestrogen has a proliferative effect justifies a trial of supplementary Progynon therapy in such cases of inflammation and bleeding. Clinical experience has shown definite results [464]. Progynon B oleosum forte is given intramuscularly in 5 mg. doses daily for 3 to 5 days, and even larger doses in severe cases [465] The result is a rapid regeneration, which when completed makes it fairly impossible for pathogens to penetrate The promising results of oestrogen treatment should not however lead to the indiscriminate use of the hormone without definite indication in every case of apparent endometritic bleeding Uterine tonics should be administered simultaneously with the oestrogen. Placental remains should be removed with a curette. In addition, if there are severe signs of inflammation the infection must be combated with sulphonamides or antibiotics.

Pyometra

Factors responsible for the appearance of pyometra in older women, such as polyps, submucous fibroids or carcinoma must naturally be removed Drainage of pus may be promoted by introduction of a drain and by lavage. The duration of treatment

may often be shortened by giving three injections of 5 mg. Progynon B oleosum forte. The rapid regeneration and improvement in circulation produced by this promote healing

Leucorrhoea

Present views of the origin of leucorrhoea have altered considerably in comparison with former opinions. Causes are divided into exogenous and endogenous factors. The uterine cavity is thought not to play any part in it On the other hand, a cervicitis is common; this is regarded as a common cause of vaginitis. External causes include contamination such as may be induced by old perineal tears, vaginal prolapse, douching or intercourse. The exudative diathesis, constitutional anomalies, psychical causes or any ovarian insufficiency are held responsible for the endogenous type of leucorrhoea which responds to hormone treatment The acid medium of the vagina normally prevents the growth of undesirable bacteria. If the biological self-cleansing mechanism of the vagina is upset, as may occur in consequence of a deficiency of oestrogens, in addition to inadequate proliferation of the vaginal epithelium there may develop an absence of glycogen in the desquamating vaginal epithelium, and hence a condition unfavourable to the growth of the normal vaginal flora (Doderlein's bacillus) Oestrogens favour the settlement of Doderlein's bacillus in the vagina, and therefore restore biological conditions in the latter [466]. For the treatment of this type of leucorrhoea due to oestrogen deficiency 2 to 3 injections a week, each of 1 mg Progynon B oleosum intramuscularly, are recommended, in the week before menstruation nothing is given In the treatment of leucorrhoea caused by gonococci (cervical gonorrhoea in the sexually mature woman) or trichomonads, oestrogens are used as an adjuvant On the other hand, supplementary hormone treatment of a purulent leucorrhoea originating in a cervical erosion is not very promising. If there is hypersecretion of the cervical glands, testosterone is advised

Atrophic senile vaginitis

Atrophic senile vaginitis is a common and usually isolated inflammation of the vaginal mucosa. The oestrogen deficit in ageing women at the menopause leads to glycogen depletion in the vaginal epithelium, and to defective resistance to bacterial infections. Oestrogen treatment (intramuscular injection of 1 mg. Progynon B oleosum once or twice a week, or 1 Progynon dragee buccally 3 times a day) often produces rapid improvement even without local treatment.

Gonococcal vulvo-vaginitis in children

Since oestrogens have been introduced in the treatment of this specific vaginal inflammation in children, significantly better results have been obtained. The vaginal mucosa of young girls responds to a single dose of 1 mg. Progynon B oleosum intramuscularly by epithelial growth, glycogen storage, increase in acidity of the vaginal secretion from a pH of 7 to 4.5, and pronounced hyperaemia. Oestrogen thus prepares the way for the curative action of penicillin or sulphonamides administered simultaneously or a little later. With this dosage, undesirable development of secondary sex characters and signs of premature puberty need not be feared [167].

Leukoplakia: Kraurosis vulvae

Leukoplakia of the vulva appears as the result of vulvar inflammation of a very long duration, especially at the menopause. This appears as irregular white plaques, on whose base carcinoma not infrequently develops. Because of the fall in oestrogen level in the blood, there is glycogen depletion of the vagina and thus inadequate protection by acid; in consequence there may arise itching eczema, discharge, erosions, or contraction of the labia and narrowing of the vagina

These manifestations used at one time to defy all therapeutic effort. Spontaneous cure is hardly possible. The introduction of

Progynon has improved the prospects of cure in this condition [74]. Intramuscular injection of one 1 mg. ampoule of Progynon B oleosum once or twice a week, or in severe cases 5 mg., is advised. Local treatment with Progynon ointment is also promising.

Chronic salpingitis

As with vaginal disorders, the effect of oestrogens can be utilized for the treatment of chronic tubal inflammation. Oestrogens lead to growth of the tubes, hyperaemia of the pelvis and the entire vascular region of the tubes, and proliferation of tubal epithelium. Administration of oestrogens often causes enlargement and dilatation of the tubes, absorption of inflammatory infiltrates, and disappearance of catarrh and tubal adhesions. During the proliferation phase after menstruation, a total of five doses of 5 mg Progynon B oleosum forte is given intramuscularly at 4-day intervals. If the tubes are already occluded by connective tissue, hormone therapy is naturally ineffective.

Female sterility

New possibilities for the successful treatment of sterility in the female have been obtained with the advent of hormones. As is well-known, it is often extremely difficult to discover the cause of this condition The prospects of successful hormone therapy depend to a large extent on the cause of the sterility.

Before beginning treatment examination of the husband's semen should be carried out. Whenever possible, when the woman is examined gynaecologically a permeability test of the tubes should be undertaken, and the optimum dates for conception calculated [168]. There is a possibility of successful outcome of hormone treatment in cases in which the sterility is due to one of the following causes uterine hypoplasia, oligomenorrhoea or polymenorrhoea, anovulatory cycle, habitual late ovulation, subliminal corpus luteum function, disturbances of thyroid activity, and finally difficulties of passage through the tubes.

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Gonococcal vulvo-vaginitis in children

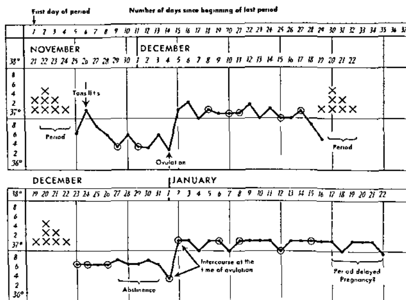
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An anovulatory cycle is characterized by the absence of the rise in morning temperature level (basal temperature) during the secretory phase, which is regularly demonstrable at this time in normally menstruating women (Fig. 49). Anovulatory bleeding and the consequent sterility respond well to oestrogens, indirectly



Schematic diagrams of a basal temperature chart during a 28½ day cycle with and without conception

× Bleeding ⊙ Intercourse (After P TOMPKINS [472])

Fig 49

via the anterior pituitary In such cases, 5 mg. of Progynon B oleosum forte is administered intramuscularly on 4 occasions between the 8th and 12th day of the cycle [74]. Good results may occasionally be obtained with Priantin (cf page 200)

In habitual late ovulation with a 28 day cycle, the follicle ruptures only after the 20th day [74]. As a result the ovum is ripe for implantation only late in the cycle, at the time of the

10*

Sterility due to uterine hypoplasia is to be treated according to the principles discussed above. This also holds good for treatment of *oligo- and polymenorrhoea.*

An anovulatory cycle is present when follicular atresia occurs with absence of follicular rupture, so that no corpus *luteum hormone is formed, and bleeding takes place from the* proliferated endometrium as a result of deficiency of corpus luteum hormone. Curettage on the first day of bleeding will reveal the cause of this pseudo-menstruation. Diagnosis has been much simplified recently [169]. Daily observation of morning temperature (basal temperature) in sexually mature women is of great value as a diagnostic aid [470, 471, 472]. In women who menstruate *regularly, there is a slight rise in temperature during the pre-*menstrual phase by 0.5—0.8° C. (0.9—1.4° F.), which is evidently related to the formation and function of the corpus luteum. The rise in basal temperature begins with the rupture of the follicle; the temperature forms a plateau at about *37.3—37.5° C. (99—*99.5° F.) during the secretory phase and falls to normal with the onset of menstruation. On the day before the rise in temperature, the latter tends to be specially low (Fig. 49). As regards the technique of measurement, it is important to take the latter in a morning with the patient fasting, before getting out of bed, so far as possible at the same time and always with the same *thermometer. It must be taken orally or rectally, and always* by the same route. The patient should be told why the temperature is to be taken so that she may make an exact note of deviations, which are often relatively small. Common infections may affect the course *of the temperature, and must be noted* (Fig. 49) [173]. Regular observation of the morning temperature during several cycles will serve to clarify the following questions: (1) duration of the proliferation phase; (2) duration of the secretory phase; (3) determination of the day of ovulation; (4) determination of fertile and infertile days; (5) differential diagnosis between secondary amenorrhoea and early pregnancy.

"rejuvenation treatment" by transplantation of endocrine glands, so much derided later. Subsequent empirical therapy with organ extracts or total gland preparations made it possible to recognize the interplay of the glands of internal secretion and the manifold nature of the causation of the climacteric. We now know that the symptoms which appear during the years of involution are due not only to a physiological atrophy of the sex organs but also to disturbances in other glands and organs, as well as to central nervous factors with their repercussions on the gonads. Hence the treatment of menopausal symptoms implies the removal of disturbances of the harmony of the entire neuro-vegetative-endocrine system

It is now known that the true cause of the mental and physical disturbances at the climacteric is the loss of the follicular hormone, which in its turn induces an increased output of the tropins of the anterior pituitary. The thyrotropic hormone of the anterior pituitary is also produced and excreted in increased quantity. The entire endocrine system, especially the anterior pituitary function, is disorganized. The loss of the inhibiting influence of oestrogen on central nervous processes leads to far-reaching disturbances The latter make a therapeutic intervention with oestrogen necessary, in order to restore equilibrium to the inter-endocrine system, and to make the signs of deficiency disappear. For this reason, oestrogen treatment constitutes causal therapy of menopausal symptoms.

The well-known manifestations of the change of life vary greatly with the individual. Their intensity depends on the extent and timing of the fall in oestrogen level in the blood They are seen as tiredness, insomnia, malaise, palpitations, attacks of vertigo, hot flushes, bouts of sweating, pruritus, eczema, arthroses, dyspnoea, irregular genital bleeding, overexcitability, loss of self-control, and depression. These manifestations of the change of life must be distinguished from the so-called premenopausal manifestations, which in the form of bleeding, tendency to oc-

menses, so that nidation of the ovum is no longer possible. Priantin treatment may be successful (cf. page 267).

The defective or shortened development of the secretory phase due to inadequate function of the corpus luteum is aided by substitution of corpus luteum hormone. In the second half of the intermenstruum, 8 injections or more must be given, each consisting of 5 mg. Proluton intramuscularly.

When the diagnosis is not clear in a case of sterility and treatment *has been unsuccessful, attention should be given to the* possibility of other causes (thyroid hyperfunction, mechanical obstruction in the uterus, nervous disturbances, etc); the possibility should be carefully considered of mental traumata within or outside the marriage.

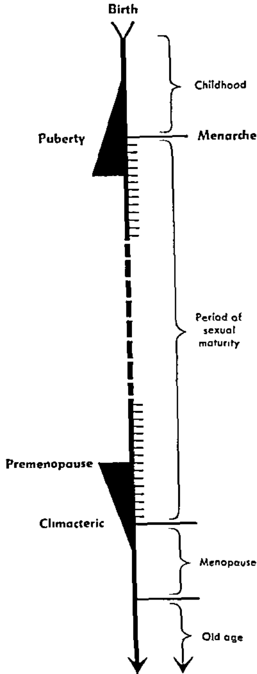
Frigidity

In connexion with the treatment of sterility, the question is often raised of a possible influence on frigidity. The causes of this condition, which is not uncommonly encountered, are chiefly of a mental nature. Women with signs of ovarian disturbance will naturally offer the best prospects for hormone treatment. If such signs are present, treatment with oestrogen may often be successful.

An aphrodisiac effect of testosterone has recently been observed; in large doses the latter causes hypertrophy of the erotogenic clitoris area [474], and also leads to activation of libido and increase in sexual activity [139]. It has also been shown that women with hyperoestrinism are particularly liable to be frigid. These are the patients who should first of all be considered for testosterone treatment.

Climacteric

Some decades ago, experimental studies showed that deficiency signs and symptoms after castration could be made to disappear by ovarian transplantation. These observations gave rise to the



Schematic diagram
Phases of function at
the beginning and the
end of the reproductive
period of the woman

(Modified from
Martius)

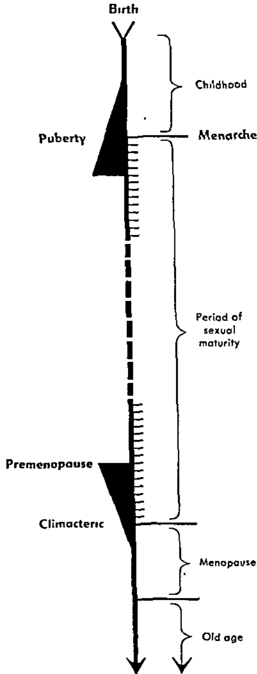
Fig 50

dema, and breast pain, are a direct expression of an enhanced oestrogenic effect. It is well known that the so-called "fading" of a woman may be in advance of her age, and may begin unphysiologically early. The early diminution in ovarian function often leads to very unpleasant happenings, which may cause difficulties in marriage and in the entourage. A distinct advantage of treatment with the naturally occurring follicular hormone is that the latter in contrast to synthetic oestrogenic substances also has a direct action on the psyche (25, 26, etc.).

Oestrogen treatment of climacteric symptoms, which often represent an almost unbearable burden, is one of the most gratifying and successful fields of employment for the hormone. According to the severity of the symptoms, one Progynon forte dragee is given buccally 2 or 3 times a day, or 10 Progynon drops are given perlingually 3 times a day, or supplementary injections of Progynon B oleosum, 1 or 5 mg., are given intramuscularly once or twice a week.

The treatment of climacteric symptoms has been greatly simplified through the introduction of ethinyl oestradiol as Progynon C. The profound effect of this agent on oral administration (cf. page 103) makes it possible to carry out treatment with success and convenience by use of very small doses. The initial dose is one tablet of 0.02 mg Progynon C daily, this being then slowly reduced to 1 tablet every 2 or 3 days. If symptoms have not disappeared after this, it is advisable to raise the dose for the time being to 1 tablet 2 or 3 times a day.

Testosterone has also been recommended recently for therapy of menopausal and pre-menopausal symptoms. This has the same type of effect as oestrogen on the hyperfunctioning anterior pituitary. For the duration of 3 or 4 months, 10 or 25 mg Testoviron should be given intramuscularly once or twice a week, or one or two Testoviron tablets of 5 mg. should be given buccally daily (175, 176, 177). Testosterone is also to be preferred for women who respond to oestrogen therapy with bleeding,



Schematic diagram: Phases of function at the beginning and the end of the reproductive period of the woman

(Modified from Martius)

Fig. 50

or who have or have had breast tumours or mastopathy or genital tumours. *Testosterone treatment of depression at the climacteric* is particularly gratifying. Treatment with depot preparations has also been recommended [178]. It is sufficient to inject 50—100 mg. *of Testoviron-Depot every two to four weeks, or if necessary* at shorter intervals. There are undoubtedly advantages in combined treatment with testosterone and oestrogens in certain cases; this treatment has recently been undertaken quite frequently. Provided that the proportions of the two hormones in the mixture are correctly chosen, the result must be good. Signs of endometrial proliferation are to be avoided. A suitable mixture is contained in the preparation Primodian. Each tablet contains 4 mg. of methyl testosterone and 0.002 mg. ethinyl oestradiol, equivalent to 1/10 tablet of Progynon C.

Castration

In 1933, Kaufmann [83] first succeeded in producing a menstrual period in a completely castrated woman (sequelae of operation, irradiation). Following his experience, 5 doses of 5 mg. Progynon B oleosum forte are given intramuscularly during the first 20 days *of an artificially induced cycle, and 5 mg. Proluton intramuscularly* each day from the 21st to the 25th day (Kaufmann's full course). The same effect can be obtained by giving Progynon C orally during the first 16—20 days in doses of up to 2 tablets 3 times a day, followed by 5 mg. Proluton i. m daily from the 21st to the 25th day.

The following total doses are needed to develop a proliferation phase *in a completely castrated woman:*

Progynon B oleosum, intramuscularly	25 mg.
Progynon dragees, buccally	180—200 mg.
Progynon C, orally	1 7—2.5 mg.
Progynon implants, subfascially . .	0 5—3.0 mg.
Progynon drops, perlingually	180 mg.

It is important to keep in mind the very different dose levels needed when choosing the mode of administration. Without attention to these differences, exact hormone therapy is impossible. Implantation therapy in the completely castrated woman deserves special mention. This mode of treatment is especially indicated for castrates By means of it a continuous supply of oestrogen is ensured over a prolonged period (cf. page 110). Since about 5—10% of an oestradiol implant is absorbed monthly [179], the above figures indicate that for oestrogen supply a Progynon implant of 10 or 20 mg can be given, and will suffice for several months. If a menstrual period is to be obtained, in accordance with cyclical rhythm, Proluton must be given intramuscularly (at least 5 doses of 5 mg.) 14 days after the implantation It must be clearly understood that inducing a menstrual period in a castrate is only of experimental or psychical value. The treatment of symptoms with small doses of oestrogen or other therapeutic methods as in the menopause is the first consideration in therapy.

The obvious consequences of castration are an atrophy of the primary and secondary sex characters, a loss of libido, and psychical changes such as are seen at the climacteric. These manifestations not infrequently lead to considerable difficulty in marriage or professional life. There is often a loss of hair, or a male hair growth with a more or less pronounced beard, together with atrophy of the breasts and a change in behaviour of an "old maid" type These occurrences are sometimes accompanied by chronic inflammation of the vagina and vulva. Excessive deposition of fat may lead to an appearance very unpleasing aesthetically. Now and then, metabolic disturbances arise, but these often right themselves again

Treatment of such conditions depends on the degree of the disturbance, the patient's age and the environment In individual cases it may be necessary to decide on the necessity for therapeutic intervention, bearing in mind the circumstances.

Pregnancy

During pregnancy many types of disturbance of endocrine origin may appear in the mother. Some of these appear shortly after conception, and may not end until long after the puerperium.

The physiology of the female sex hormones and their effects and purpose in the organism of the pregnant woman are now known (cf. Figs. 17—19). Very recently, attention has again been drawn to the relations existing in pregnancy between the sympathetic and oestrogens on the one hand, and the parasympathetic and corpus luteum hormone on the other [180]. A pregnancy can develop undisturbed only under the protective action of the parasympathetic and the corpus luteum hormone.

If conception occurs, the corpus luteum is retained (corpus luteum of pregnancy) and continues to form progesterone. This hormone causes relaxation of the uterine musculature and withholding of menstruation, conditions which make possible the steady and physiological growth of the ovum From about the fourth month onwards the influence of oestrogens again becomes significant. This hormone is particularly necessary for uterine growth. The pregnancy can develop further without disturbance only if both hormones are present in adequate amounts. In the later months of pregnancy, as already stated, the placenta plays a very great part in the production of these female sex hormones and the gonadotropic hormones. Because of this endocrine activity of the placenta, it may even happen that operative removal of the ovaries during pregnancy leads to no disadvantages as regards the latter.

The high content of chorionic gonadotropin in the blood and urine of pregnant women has been used since 1928 as a urine test for pregnancy (Aschheim-Zondek reaction). Also because of the chorionic gonadotropin, injection of urine or serum from a pregnant woman into a frog leads to spermatogenesis and discharge of sperm (toad or frog test) [380, 381]. The earthworm ap-

pears to be relatively insensitive to chorionic gonadotropin, but is perhaps suitable for biological determination of gonadotropic hormones [481, 753].

Pruritus

Pruritus in pregnant women is considered to be a consequence of the cessation of maturation of follicles in the ovary [482]. Other authors believe that this pruritus is due to the fact that during pregnancy increased amounts of oestrogens (cf. page 35 and Fig 19) circulate in the blood in combined and not in active form [483, 484]. Even severe cases can be successfully treated by giving 1 or 2 injections a week of 1 or 5 mg. Progynon B oleosum intramuscularly. Good results from progesterone therapy have recently been reported in pruritus of non-pregnant women [485]. It has been found empirically that 2—6 injections, each of 5 mg. Proluton i m., lead to cure.

Habitual and threatened abortion

It is well known that there are many possibilities as regards the aetiology of a spontaneous abortion. It is frequently assumed that the principal cause is a subliminal level of corpus luteum hormone [486] The supply of corpus luteum hormone has a direct protective effect on the gravid uterus, especially at the beginning. In deciding when to begin treatment it is important to bear in mind that experience has shown that the danger of *abortion is greatest at the dates of the expected periods*, and also at about the fourth month of pregnancy It is therefore suggested that 5—10 mg Proluton be injected intramuscularly twice a week, or that 5 mg. be given daily on 3 successive days at the time when menstruation would otherwise have occurred. Treatment must be continued for at least 4 months

Particularly good results have been obtained in habitual abortion by the use of implants. One or two 100 mg Proluton implants are inserted subfascially at the beginning of pregnancy,

their effect extending for about 3 to 4 months. If it is required to obtain a rapid effect, 5 or 10 mg. Proluton may previously be injected intramuscularly. Treatment of threatened abortion, *which is often the consequence of physical stresses and* strains, involves substantially higher doses of progesterone, which are best injected because of the need for rapid effects. Timely injection (10 mg. Proluton i.m. once or twice a day, and/or 20 mg. Proluton intravenously) and hence rapidity of effect are often the deciding factor in success [187]. Progesterone medication must be tapered off and not suddenly interrupted. Spasmolytics and rest in bed aid the effect of progesterone. In threatened abortion after bleeding has ceased, implantation treatment may also be used.

Recently the belief has grown that similar results in the therapy of abortion can be obtained with large doses of oestrogens [188]. Apart from the fact that oestrogens promote uterine growth, they are thought to increase production of progesterone indirectly by stimulating the placenta to increased endocrine function [189]. Because of its high oestrogen content, Progynon M is particularly suitable for such treatment For prophylaxis of habitual abortion, at least 1 tablet of Progynon M should be given 3 times a day, and from the 4th month 2 tablets, each of 0.2 mg., 3 times a day. *In threatened abortion, the minimum daily dose* is one 0.2 mg. tablet 5 times a day [113, 116].

Toxicoses of pregnancy; Diabetes

During pregnancy, so-called "toxicoses" appear, such as dermatoses, eczema with pruritus, and vomiting of pregnancy [182]. Although the hormone relationships have not been completely clarified in these cases, the pathological lesions are very often the results of an endocrine dysfunction. Method of treatment and dosage should be chosen in each case on the basis of the history and the findings on examination. The dermatological conditions require substitution of oestrogens In vomiting of pregnancy a trial of corpus luteum therapy may be made [190, 191, 192]

It has recently been shown that desoxycorticosterone acetate in sufficiently high dosage exercises a progesterone-like effect. It has also been shown that in hyperemesis gravidarum adrenal cortical function is deficient. Because of this, and in view of the effects of adrenal cortical hormones already described, Primocort treatment of e m e s i s and h y p e r e m e s i s gravidarum can be recommended, especially if h y p o t e n s i o n is also present [493, 494]. Results of such treatment are uniformly promising, although no final pronouncement can yet be made (cf. page 193). Pregnant women with diabetes have a particular tendency to toxicoses in the last months of gestation. In a not inconsiderable proportion of cases, the foetus, which is often overdeveloped and oversized, dies. The cause is thought to be an excessive output of chorionic gonadotropin [762, 763]. Very good results in terms of saving of foetal life have been obtained by continuous treatment with ethinyl oestradiol in large doses throughout pregnancy [413, 764].

Primary uterine inertia and excessive prolongation of pregnancy

Uterine inertia at the end of pregnancy is not uncommon, and may be a cause of prolongation of pregnancy. It is supposed that labour begins because of an interplay of oestrogens, corpus luteum hormone, the pituitary, and the placenta with its endocrine activity, and because of the effects of all these hormones on the uterus [74]. On the basis of animal experiments it has been shown that oestrogens first make the uterus capable of responding to the posterior pituitary hormone oxytocin by rhythmical contractions, in other words, they again sensitize the uterus in increasing measure It is therefore logical to treat primary uterine inertia with oestrogens as well as the posterior pituitary hormone oxytocin [495, 496].

When the ovum has died, oestrogen medication leads to the expulsion of the foetus, because the placenta has ceased to function and to form oestrogens [497]. The dead foetus is more readily

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become necessary because of abscess formation, administration of oestrogens will lead to rapid closure of any milk fistula which may arise.

Attention has already been drawn to the mechanism of action of the hormone in the physiological section, in explanation of these methods of treatment Complete clarification has not as yet been reached. Some authors believe that the oestrogens do not act indirectly via the pituitary but locally, overcoming or preventing stasis by hyperaemizing action [76]. Testosterone also suppresses lactation, but only in very large doses (50 mg. daily for 8 days) [501].

Heterologous hormone therapy in the woman

Heterologous hormone treatment (treatment with the hormone of the opposite sex, sometimes misleadingly referred to as "paradoxical" hormone therapy) is finding more and more place in gynaecology for certain indications, after the experiences of the last 15 years. This refers to the employment of male sex hormone in women. It has already been mentioned on page 54 in the discussion of the details of possible treatments. This type of hormone therapy is not so paradoxical as it may appear to some persons at first glance, since relatively large amounts of male sex hormone are formed in the adrenal cortex even in women (cf. page 41) The male sex hormone is probably required in the female organism to maintain endocrine balance

It has been shown that the male sex hormone prevents the appearance of castration changes in the pituitary of both male and female castrated rats, and inhibits the folliculotropic function of the anterior pituitary [81] Male sex hormone has an inhibiting effect in the female organism on the controlling centre for hormone correlation in the diencephalon. It limits the output of follicle-stimulating hormone from the anterior pituitary. In consequence of this less oestrogens are produced. and hence with large doses ovulation is prevented. It also inhibits to a large ex-

expelled if pregnancy is advanced and the period since foetal death is short.

Premature delivery

Since the cause of premature delivery is in the first place probably a vegetative and generative insufficiency of the ovary combined with hypoplasia of the uterus, timely hormone treatment, especially of women with hypoplasia, may be considered necessary in the prophylaxis of prematurity. The frail condition of premature children is in part ascribed to the fact that oestrogens are prematurely withdrawn from the immature child. Very recently there have been reports of the suitability and significance of treatment of premature children with small doses of oestrogens. Oestrogen therapy leads to an increase in weight and to improvement in the extrauterine conditions for premature children [498]. Testosterone may be employed more effectively because of its influence on metabolism. By inhibition of protein catabolism (see page 53) a considerable increase in weight is obtained [499, 500]. Desoxycorticosterone has also been recommended (see page 198)

Suppression of lactation, Mastitis

If because of stillbirth or miscarriage or infectious disease (e. g. tuberculosis) the entry of milk into the breasts must be prevented, treatment with oestrogens is indicated. Progynon C can be conveniently administered by mouth, and in total doses of 0.7 to 1.0 mg. divided in decreasing amounts over six days leads to a rapid and satisfactory result (cf. page 30).

Inflammations in the breast are usually treated with sulphonamides or antibiotics. They respond, however, if they are due to stasis, to oestrogen treatment (2 doses of 5 mg Progynon B oleosum forte intramuscularly with a 2—4 day interval), probably because of an action on the anterior pituitary with inhibition of the lactotropic factor. If, however, surgical intervention has

tent the peripheral effect of oestrogens, and reduces the blood supply to the endometrium (see Fig. 51).

The facts mentioned above indicate the fields of employment of testosterone in women [502, 751]. Pathological effects of an excess of oestrogen and also of an excess of gonadotropic hormones can be suppressed or normalized by male sex hormone [503]. The following disorders are involved: *polymenorrhoea*, *hypermenorrhoea*, cystic glandular hyperplasia, and premenstrual symptoms [504].

Excessive and undesirable activity of oestrogens may be caused by increased or long-continued, continuous production of this hormone. This is the aetiology of cystic glandular hyperplasia (cf. page 137), in which oestrogen production is the result of persistence of a follicle or of a hormone-secreting tumour. Symptoms of excessive oestrogen activity may also appear if the degradation of the hormone in the liver is disturbed [505]. There is also a transient form of excess oestrogen activity, appearing in the premenstrual phase and manifesting itself as mastodynia (cf. page 141), dysmenorrhoea (cf. page 139) and neurovegetative signs, as well as psychical changes. It is particularly common in the premenopause. Testosterone does not completely overcome the peripheral effect of oestrogen in these cases, but it inhibits the latter considerably. If 25 mg. Testoviron is given intramuscularly 2 to 4 times during the last 10 days before the beginning of the period, it is usually possible to stop premenstrual symptoms, provided that there are no organic changes. A combination of testosterone and progesterone is specially effective in these conditions. An injection of Testoluton is given on 3 occasions within the last 10 days before the period is expected [153].

Uterine fibroids, Endometriosis

By continued supply over a long period of large doses of oestrogens to guinea-pigs, myomatous tumours were produced in the stomach, uterus, and other organs with smooth musculature

Knowledge of the inhibiting effect of testosterone on the anterior pituitary thus led to successful therapeutic trials with this hormone. The large number of women with fibroids (according to Schröder about 22% of all women between the ages of 36 and 55 years) shows the great significance of this disease in practice. With intramuscular injections of one 25 mg. ampoule of Testoviron daily or every other day, for one week before and d u r i n g the period to a total of 200—300 mg., there is often regression of the tumour, cessation of bleeding and disappearance of subjective symptoms [506, 507]. Treatment with Testoviron-Depot is very simple and effective. If this preparation is employed, it is sufficient to inject 100—250 mg. Testoviron-Depot intramuscularly every 3 or 4 weeks. With this dosage there is no danger of virilization. By serial examinations during the treatment, the success of the latter can be assessed, and the need for operation if necessary recognized.

The same procedure is used in metropathies, endometriosis and mastopathies [508, 509, 510, 511]. The question of operation or irradiation must always be borne in mind in these cases.

Carcinoma of the breast

The results of heterologous hormone treatment of mammary carcinoma are not uniform. The cause probably lies in the complexity of hormonal relationships which are involved in the physiological development of the female breast [148, 118].

It has been the experience of many research workers that with androgens a functional castration may be achieved [147, 149], as shown in animal experiments, which can lead to a fall in the carcinoma rate in high-cancer-strain mice.

Results of treatment are particularly encouraging in cases of breast carcinoma with metastases in bone, in which the patient is soon freed from pain and recalcification often occurs [512]. Testoviron-Depot is specially suitable for long-term treatment. One ampoule of 250 mg. is injected intramuscularly every two weeks,

The frequently debated diagnostic value of a rise in alkaline phosphatase in the blood should be mentioned in this connexion. Determination of this blood level has not so far proved of value in the early diagnosis of the condition. A fall in serum phosphatase is however to be regarded as a sign of regression of metastases and a steady improvement in the disease picture [517, 518].

Genital carcinoma

Heterologous hormone treatment of genital carcinoma does not give such good results [746]. Carcinoma of the body of the uterus is probably more affected than is the squamous epithelial cancer of the portio vaginalis [519]. So far, clinical results have not exceeded the demonstration of a general tonic, palliative and euphorizing effect [520, 521]. Hormone treatment also appears to lead to greater tolerance to X-ray irradiation [522]. Progesterone administration has also been suggested at times as an adjunct to other procedures [738 740].

Preclimacteric

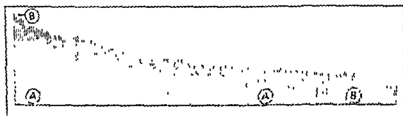
Heterologous hormone treatment of premenopausal or preclimacteric symptoms has recently been discussed. It is based on the antagonism of testosterone to oestrogens (cf. hyperfolliculinism or hyperoestrinism page 84). The possibility of using this hormone has already been mentioned on page 160 [475, 476, 477].

and after improvement sets in every 3 weeks. Even in the early days of treatment, subjective improvement is demonstrable in many cases, with alleviation of pain and general euphoric mood. The physician must choose his mode of treatment according to the individual case. It is advisable to continue treatment for as long as possible, so as to prolong the period of remission. Experience so far suggests that life is prolonged on an average by 8 months. Methylandrostenediol, which has very little virilizing effect even in high doses, has recently been strongly recommended [116, 513]. *It is specially indicated for women with a tendency to spontaneous virilism.* Fifty to 100 mg. should be injected intramuscularly three times a week. This treatment must also be continued for as long as possible, but is probably not as effective as Testoviron-Depot.

On the basis of Anglo-Saxon experience mammary carcinoma in women over 60 years old, *i. e.* beyond the menopause, is also treated with oestrogens or with corpus luteum hormone [118, 741]. It is not yet possible to explain the mode of action of the oestrogens. Such treatment has proved successful, especially in cases with soft-part metastases[514]; in these cases it is distinctly superior to testosterone. Ethinyl oestradiol is particularly suitable because of its powerful oestrogenic effect. The minimal dose is 1 tablet of 0.2 mg. Progynon M 3 times a day for 3 to 6 months or longer [515, 516, 745]. On many occasions significantly higher doses have been used, e. g. 3 mg. (15 tablets) a day, treatment being continued for as long as possible, as with testosterone It has been observed that large doses of progesterone have an androgenic effect Since, however, testosterone is much more effective than progesterone, the administration of very large doses of Proluton intramuscularly is necessary. Particularly good results are said to have been obtained in adenocarcinoma [118]

In every suitable case, amputation of the breast, X-ray irradiation, and X-ray castration should be carried out according to the approved lines.

the "male climacteric" [523]. After a brief period of tiredness lasting only for a few days, employment of testosterone leads not only to subjective improvement but also to objectively demonstrable increase in performance, which restores the pleasure of work and the capacity to work. Physical well-being, feeling of freshness, and mental elasticity improve in remarkable manner after testosterone administration, so that it is perfectly justifiable to expect a general tonic and objectively demonstrable effect



Increase in physical performance due to testosterone, shown by ergographic curves obtained by lifting and letting fall a 2 kg weight The subject was a 63-year-old man.

Lower graph. before treatment

Upper graph after treatment with testosterone: 44% increase in performance shown

(After Veil and Lippross)

Fig. 52

from this hormone therapy. The influence on cardiac output in men with a tendency to angina is particularly marked [524]. Clear and unequivocal tests have shown that the sex hormones not only have a physical effect but also a mental one, and that the observed effects are not due to suggestion or imagination [525, 338]. These studies showed that administration for several weeks of small doses of hormone every day increased mental elasticity to such an extent that certain tasks, such as arithmetical problems, could be significantly better dealt with than before the intake of hormone. The latter does not however constitute a

Therapeutic Use of Sex Hormones in Men

The physiological and pharmacological effects of testosterone were dealt with in the section on "Chemistry, physiology and pharmacology of the male sex hormones" to facilitate understanding of the therapeutic effects. The possibilities for therapeutic use include the following:

In 1911, vasoligation (tying of the vas deferens) was first carried out on senile rats. It produced a tonic effect not limited to the sexual apparatus but involving the whole organism. Attempts at gonadal transplantation carried out later on men had a favourable effect on sexual deficiencies, and in addition caused disappearance of a number of vague symptoms, such as are known from the descriptions given by men in the years of involution. When testosterone was synthesized, the data collected up to that time suggested abundant possibilities for the use of the hormone in therapy.

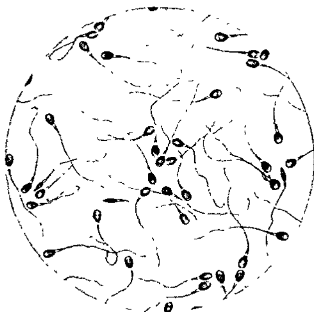
Manifestations of mental and physical exhaustion, Male climacteric

Signs of mental exhaustion and of diminution of bodily elasticity are in the foreground of the indications for testosterone. Disturbances which appear in men of all classes during middle age and later are manifested as insomnia, failing power of concentration, diminution of attention and of memory, lack of physical tone, apathy, ill-humour, irritability, depression and so on. The whole symptom complex, which may be further complicated by autonomic nervous system disturbances, circulatory symptoms, anginal symptoms, skin disorders and many other complaints, is called

well as in severe states of exhaustion, 10 mg. Testoviron should be injected intramuscularly, at first daily. From the fifth injection on, two or three 10 mg. ampoules a week will suffice.

Impotence, Sterility

After the good results obtained with testosterone in the male climacteric, it was reasonable to expect similar success in the



Normal spermatogram (After Boenig (769))

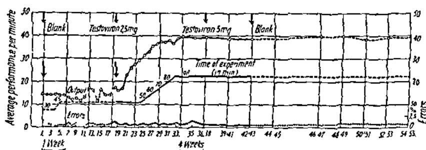
Fig 54

treatment of impotence and sterility. Unfortunately, the results in these cases are not so definite. The cause of this is the great diversity of origin of these disturbances.

Fertility depends on spermatogenesis alone (external secretion of the testis); potency does not depend exclusively on the internal secretion of the testis Hormone insufficiency is certainly

temporary stimulus. The important point is that after hormone therapy *is discontinued* the improvement in performance is maintained [525].

Several scientists have given experimental proof of the removal of physical and mental disturbances by testosterone [25, 26, 526],



This illustration reproduces two curves: one shows the performance or output, the other the percentage of errors of calculation. The left vertical line shows the average number of calculations made per minute, the right the percentage of wrong answers, and the horizontal the succession in time of the experiments The days on which performance was checked are indicated. The duration of each experiment in minutes is also shown

(After Düker)

Fig. 53

confirmed this clinically, and also shown that libido and potency can be restored by giving this hormone [127, 527 etc.].

The dosage of testosterone in cases of mental fatigue and states of psycho-physical exhaustion depends on the needs of the individual patient. *In general it is advisable to give one or two 5 mg.* tablets of Testoviron daily during the male climacteric, they should be taken regularly buccally for at least 4 to 6 weeks. The use of Testoviron T, which is an alcoholic solution for rubbing into the skin in a dose of 10—15 drops 3 times a day, has also proved valuable. In more severe cases it is advisable to employ Testoviron-Depot in doses of 50—100 mg. every 2 to 4 weeks. Before and after severe operations and after severe illness, as

recommended. In many cases, larger doses of up to 4 injections of 25 mg. a week are needed to restore the ejaculate to normal.

It has already been repeatedly stressed that the gonads are under the stimulating influence of the anterior pituitary gonadotropins. For this reason, the spermiogenetic factor (follicle-stimulating factor) of the anterior pituitary is also brought into action to reinforce the therapeutic effect. In resistant cases Priantin is employed. This contains the spermiogenetic factor and is administered intramuscularly 2 or 3 times a week (in doses of 1,000 or 5,000 i. u. up to 10 injections) After an interval of several weeks the course of injections should be repeated. Treatment should be continued over several months. Combined treatment with Testoviron and Priantin has also been recommended. After several weeks of treatment with Testoviron, 1,000—5,000 i. u. Priantin is given i. m 2 or 3 times a week [530].

Ejaculatio praecox

Premature ejaculation is one of the symptoms of sexual neurosis. This disturbance often accentuates the state of depression which is already present in the patient. Testosterone has been used successfully in the treatment of this condition. It improves the mood and overcomes the exhaustion which is often present. Success may be obtained by injection of one ampoule of 10 mg. Testoviron i m. 3 to 5 times a week; for after-treatment one 5 mg tablet Testoviron should be given buccally 3 or 4 times a day for a prolonged period. Combination with oestrogens has recently been recommended [717].

Induratio penis plastica

This condition, which is so extraordinarily troublesome, has so far presented an insoluble therapeutic problem. X-ray or radium therapy is well known to be unsatisfactory. After 3 to 4 weeks of oestrogen treatment the painful erections become less and less frequent, and treatment may be gradually tapered off [531, 532] (cf page 248).

only partial cause of impotence. Psychosexual factors, environ mental influences, organic disturbances, infections, and chronic intoxications, such as morphinism, play a considerable part in causation. Mental and physical stress may also lead to reduced ability to perform the sexual act. It is absolutely essential to ascertain the exact cause of impotence before treating it with hormones. If the impotence is due to a subliminal hormone output from the testis, treatment with one 10 mg. ampoule of Testoviron intramuscularly 3 to 5 times a week is often successful The course may be continued after an effect has begun by giving 5 mg. Testoviron tablets buccally or Testoviron T transcutaneously.

As with impotence, it is necessary to discover the cause of sterility before treating it; repeated examinations of semen are necessary in every case. Testicular biopsy gives a better impression of the behaviour of the testicular epithelium. Azoospermia (found in 10 to 30% of sterile marriages), necrospermia and aspermia may all be the cause of this serious disturbance.

Since *aspermia* is usually the result of inflammatory processes in the epididymis, or vas deferens (e. g. gonococcal infection), or even of complete destruction of the testicular parenchyma, it does not generally respond at all to hormone treatment. The chance of overcoming a sterility due to severe trauma or damage by X-rays or radium is naturally equally slight.

In contrast to this, endocrine treatment of *azoospermia* and *necrospermia* offers certain prospects of success. In the experience of many authors this is particularly true of necrospermia, in which the immobility of the spermatozoa is the cause of the sterility [528, 529]. In both cases an attempt should be made at treatment, since the generative and the endocrine functions of the testis are so closely related that overcoming an endocrine insufficiency often leads to a lasting result. Two or three intramuscular injections a week, each of 10 or 25 mg. Testoviron, are

Nocturnal enuresis

The treatment of nocturnal enuresis with testosterone, or in girls with oestrogens, often leads to improvement or even complete disappearance of the condition

In many cases it is presumed that the cause of the bedwetting lies in a segmental biological inferiority of the bladder sphincter, the prostate or even the testes (or ovaries). Treatment requires total amounts of 90 to 120 mg. Testoviron i. m. or 9 to 12 mg. Progynon i. m. (10 mg. *Testoviron i. m. once or twice a week*, or 1 to 2 mg. Progynon i. m.). Side-effects of the nature of a premature puberty regress after treatment ceases [534, 535].

Dystrophia adiposo-genitalis

The anterior pituitary gonadotropins control the sex hormones and affect both development and function of the gonads, which in their turn form testosterone or oestrogens. Disturbance of this mechanism appearing early in life leads to dystrophia adiposo-genitalis, which usually develops between the 10th and 12th years of life and occurs in both sexes.

An occasional cause of this syndrome is an adenoma of the pituitary. inflammation of tumour formation in the vicinity of the *pituitary may also lead secondarily to this condition In the latter* case a whole series of symptoms indicate quite clearly the presence of an intracranial lesion, operation or irradiation is necessary.

In addition to the marked obesity and other metabolic disturbances (in carbohydrate metabolism, water balance, etc) in this condition, a prominent feature of the clinical picture is the developmental disturbance of the genitalia. If cerebral symptoms are absent, treatment with sex hormones or anterior pituitary hormones often leads to a successful result. Medication should continue for one or two years, with intervals. It is advisable to employ Primogonyl and testosterone, or oestrogens in the case

Infantilism, Cryptorchidism, Hypogenitalism

As in women, absence or deficiency of the homologous sex hormone leads to infantilism (underdevelopment of the entire habitus) of various degrees in the male. In many cases the infantilism is associated with cryptorchidism. A primary hypogenitalism is distinguished. In this there is usually irreversible damage or inferiority of the gonads A secondary hypogenitalism is also known in which testicular degeneration has appeared as a result of deficient anterior pituitary function.

In infantilism in childhood, mental and physical general development is disturbed, and the appearance of secondary sex characters is delayed. In addition, signs of myopathy, hypersensitivity, etc., are described.

Testosterone medication not only increases the size of the testes and the scrotum, but also promotes considerably the general mental and physical development Cryptorchidism responds well to testosterone medication provided that the descent of the testis is not prevented by anatomical changes. Treatment should take place between the 10th and the 12th year, so that irreversible damage to the retained testis is not done as a result of the pressure and particularly the heat in the lower abdomen, and so that the optimum time for surgical fixation of the testis in the scrotum is not missed Libido and potency later become normal if treatment is successful Employment of Primogonyl has frequently been recommended in cryptorchidism, since this preparation specially stimulates the Leydig interstitial cells and thus induces increased output of male sex hormone [533]. Primogonyl is specially indicated if hypofunction of the pituitary or the diencephalon appears to be present

Recently, animal experiments have led, in some cases of marked infantilism, to local employment of testosterone and its implantation into the scrotum. This is followed by an impressive increase in size of the testes, accompanied by development of secondary sex characters [118, 405, 406]

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of girls, the sex hormones being possibly used in the form of implants. The use of dietetic measures should never be neglected. Disturbances of fat metabolism of central origin do not always respond to treatment (see page 203).

Manifestations of castration

The success of hormone treatment of castrates continues to be confirmed. The results to be expected from treatment of castrates in the years of development are naturally not so good as with castration later in life, when after normal physical and mental development gonadal function is lost because of operation, trauma, syphilis, gonorrhoea or other cause. The loss of the testes and the consequent absence of male sex hormone, except for that formed in the adrenal cortex, leads to general disturbances of water balance, to fall in metabolic rate and hence to fat deposition, to mental changes, to physical weakness, to loss of libido and potency and other concomitants, which make hormone administration absolutely necessary. Results of treatment of late castrates are excellent. The maintenance dose varies with the individual. Whereas at the beginning of treatment about double the dose is needed, the maintenance dose in full castrates are approximately the following

Testoviron, intramuscularly	5—10 mg. daily
Testoviron tablets, buccally	7—15 mg daily
Testoviron T, transcutaneously	10—20 mg. daily
Testoviron implants, subfascially	about 0.5—1 mg daily
(with implantation of 2 implants, each of 100 mg.)	
Testoviron-Depot, i. m. 250 mg. over 3—5 weeks.	

Prostatic hypertrophy

About 70% of all men over the age of 60 suffer from the well-known symptoms of prostatic hypertrophy. Some authorities conclude from this that the condition is connected with the slow failure of androgen production. It has also been shown in animal

experiments that adenomata of the prostate can be produced with oestrogens [90]. It has also been suggested that the disorder is connected with the increased function of the anterior pituitary during the male climacteric [105, 536, 537]. Testosterone therapy is indicated only when carcinoma of the prostate can be excluded with certainty, and when the disorder is in an early stage [538]. Examination of prostatic secretion by the Papanicolaou method to confirm the diagnosis is often advised [539]. The general range of dosage is set out in the Suggestions for Dosage on page 260. Mild cases may be favourably influenced for years (improvement in general condition, diminution in residual urine). In cases suitable for operation, a course of hormone treatment will increase the chance of success. Patients suitable for operation are often in poor general condition, and already have impairment of the renal parenchyma. In these cases, testosterone prevents degenerative changes in the renal tubules because of its renotropic factor (cf. page 54), and has a tonic and protein-sparing action. Testosterone has also been employed successfully post-operatively [90].

Certain authors have for a long time been of the opinion that prostatic hypertrophy can also be treated by oestrogens, given either alternately or even simultaneously with androgens [92, 540]. These proposals are however still so very diverse that it is not yet possible to make a statement on them In deciding whether a case of prostatic hypertrophy should be treated with testosterone or oestrogens, the age of the patient and the reliability of the diagnosis (benign as against malignant lesion) should be the decisive factors. In younger patients it will be more difficult to decide in favour of oestrogens, whereas on the other hand any case in which there is a suspicion of malignancy must not be treated with testosterone. When the diagnosis of adenoma is certain, it is sufficient to give one or two 0.2 mg. tablets of Progynon M daily. In carcinoma however a higher dosage is required (cf. page 174). A warning must be given against indiscriminate hormone treatment, since this entails the risk that the

patient may pass into an inoperable state. After operation, testosterone treatment is indicated because of the general stimulating and tonic effects.

Prostatic carcinoma, heterologous hormone therapy

Growth and hardening of a prostatic tumour always arouse suspicion of carcinoma. Because of the poor results of operation in such cases, oestrogen therapy is preferable.

Prostatic carcinoma arises in the neighbourhood of the capsule. According to various authors, the tissue found there is in biological opposition to the proliferation of periurethral glands stimulated by female sex hormones in prostatic hypertrophy [541, 118]. Definitive cure of the tumour by oestrogen administration is impossible. The patient's general condition is however improved significantly, the tumour shrinks in size, and the pain due to metastases disappears. In the literature there are also descriptions of radiologically confirmed recalcification of the metastases in bone. These results and the prolongation of life which has already been demonstrated ([118]; cf. Figs. 55a and b and 56) are of such great value that the patient can put up with the appearance of side-effects, such as feminization changes and in particular a frequently painful swelling of the breast [118, 542].

Treatment entails giving relatively large doses of oestrogens for t h e r e s t o f t h e p a t i e n t ' s l i f e. The supply of hormone must not be interrupted. The appearance of the so-called nipple reaction (swelling and pain in the breast, and even in some cases secretion of colostrum) is insignificant in comparison with the advantages of this technique. When a specimen of prostate obtained by operation proves to be carcinomatous, and the appearance of metastases is therefore to be feared, oestrogens must always be given postoperatively. Progynon M, Progynon implants and possibly Progynon B oleosum are available for treatment. Experience so far in the treatment of prostatic carcinoma with Progynon M suggests that the dosage given on page 260 is ade-



Osteoplastic metastasis in the neck of the left femur in a case of untreated prostatic carcinoma Patient E J, born in 1888, radiograph 4 Dec. 1947.
(From the Urological Department of the Municipal Hospital, Berlin-Westend Director Dr Hellenschmied)

Fig 55a

the human organism is mirrored in the great number of diseases which respond in some degree to treatment with sex hormones; of these, a number will merely be mentioned in the Suggestions for Dosage (pages 220 et seq.).

Vascular disturbances

Observations in recent years have shown a definite spread and increase in incidence of vascular disease. In view of the social significance of these disturbances to health, it constitutes a definite therapeutic advance to record that sex hormones often completely restore capacity for work and fitness to persons of working age. The hyperaemic effect, the influence on function of muscle and central nervous system, the promotion of circulation in certain organs with smooth muscle, and the spasmolytic effect on the musculature of vessels suggest a connexion between circulation and sex hormones. The findings of animal experiments and the common occurrence of circulatory disturbances closely linked to sex confirm the close relationship of sex hormones to vascular disturbances [550]. Apart from other therapeutic methods, the following disorders justify a trial of treatment with hormones: endangiitis obliterans, Raynaud's syndrome, acrocyanosis, dead fingers, intermittent claudication, acroparaesthesiae, frostbite, coronary spasm, angina pectoris, migraine and leg ulcer (cf. page 232). After administration of 0.5 mg. *ergotamine tartrate to rats for 6 days, extensive necrosis of the tail appears* (see Fig. 57); in control animals pre-treated with 1 mg. oestradiol benzoate this is absent. In clinical practice, analogous effects of sex hormones have been obtained in human peripheral circulatory disturbances [550]. Signs of hormone deficiency are often demonstrable in the conditions listed above. The vasodilator action of the sex hormones is desirable and therapeutically necessary in all of the cases mentioned above. The earlier hormone treatment begins, the less likely are irreparable structural changes in the vessels to appear, and the greater are the prospects of success. Many authors have reported

details of therapeutic technique, dosage and results. These experiences have been taken into account in the Suggestions for Dosage on page 232



After administration of 0,5 mg ergotamine tartrate to rats for 6 days
On the right, necrosis of the tail, on the left, no appearance of necrosis
with simultaneous administration of 1 mg. oestradiol benzoate.
(After Ratschow)

Fig 57

are present, treatment with small doses of oestrogens, or even testosterone, is advised ([561]; cf. page 171). In preparation for operations for bladder fistulae, 1 mg. Progynon B oleosum is given daily intramuscularly for 8 to 10 days [536, 565].

Depression

Sex hormones have been extensively employed to combat depression. *Treatment with male sex hormone is of particular* significance, because the latter very often favourably influences mood in both sexes [139] (cf. Climacteric). Results are probably to be explained by central effects and immediate stimulation of the ganglion cells in the brain. Extensive experience has however shown that direct effects on the brain can only be expected from true, naturally occurring hormones ([25, 26]; cf. page 16).

Endocrine arthropathies

Treatment of joint disorders affected by hormones must again *be stressed. Recent literature* [156 190 192] *not only demonstrates* the difficulty of laying down indications for hormone therapy, but also shows the possibility of new methods of treatment (cf. adrenal cortical hormones, page 70). In disorders of joints associated with the climacteric, especially the osteoarthritis of knee so commonly encountered, excellent results of oestrogen treatment have often been described The dosage recommended *is set out in the Suggestions for Dosage* ([566 567 568 569 570]; *cf.* page 53).

Diseases with protein depletion

As already mentioned in the discussion of hormone therapy of cancer (page 53), testosterone in particular, and apparently also the non-virilizing methylandrostenediol, have an effect favouring protein *anabolism* [571 572 573]. *Therapeutic effects depending* on this anabolic effect may be expected in all forms of protein depletion (chronic infections, cachexia). The good results in

osteoporosis [130, 591] also depend on this effect. Apart from protein, the building up of phosphorus, potassium, calcium and salt is also promoted.

An important indication for both these substances is the treatment of premature infants.

Further indications

In addition to the above extragenital disorders which respond to sex-hormone treatment, the successful treatment of the following disturbances is also described in the literature: hyperthyroidism [574, 575, 576, 577]; diabetes mellitus [578, 579, 580, 127]; diabetes in the aged [227]; blood disorders [581, 582, 583, 584]; malnutrition [585], bronchial asthma [586, 587]; deafness in the ageing, internal ear disturbances and otosclerosis [588, 589, 590]; disturbances of wound healing [565]; and loss of hair [592, 593]. Hormone dosage should always be adapted to the indication and to the needs of the organism (cf. Suggestions for Dosage, page 220)

Hormones and the Aetiology of Cancer

The hotly disputed question whether cancer may arise through administration of sex hormones is due to the chemical similarity of these substances with the aromatic hydrocarbons, whose cancerogenic effects are well known and have been proved experimentally. Authoritative writers have repeatedly taken up this question and stressed that the sex hormones have no cancerogenic properties. Sex hormones may, if there is a suitable predisposition, merely act as conditional carcinogens [591, 595, 596] The "conditional carcinogenic" effect of sex hormones will however appear only if there is a special predisposition to cancer or "cancer taint" [765]. This is understandable if it is recalled that sex hormones have a proliferative action on sexually differentiated tissue This physiological action affects both normal cells and cells with a "predisposition to cancer." Only the administration of excessively high doses of hormone over pro-

are present, treatment with small doses of oestrogens, or even testosterone, is advised ([564]; cf. page 171). In preparation for operations for bladder fistulae, 1 mg. Progynon B oleosum is given daily intramuscularly for 8 to 10 days [536, 565].

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An important indication for both these substances is the treatment of premature infants.

Further indications

In addition to the above extragenital disorders which respond to sex-hormone treatment, the successful treatment of the following disturbances is also described in the literature: hyperthyroidism [574, 575, 576, 577]; diabetes mellitus [578, 579, 580, 127]; diabetes in the aged [227], blood disorders [581, 582, 583, 584]; malnutrition [585]; bronchial asthma [586, 587]; deafness in the ageing, internal ear disturbances and otosclerosis [588, 589, 590]; disturbances of wound healing [565]; and loss of hair [592, 593]. Hormone dosage should always be adapted to the indication and to the needs of the organism (cf. Suggestions for Dosage, page 220).

Hormones and the Aetiology of Cancer

The hotly disputed question whether cancer may arise through administration of sex hormones is due to the chemical similarity of these substances with the aromatic hydrocarbons, whose cancerogenic effects are well known and have been proved experimentally. Authoritative writers have repeatedly taken up this question and stressed that the sex hormones have no cancerogenic properties Sex hormones may, if there is a suitable predisposition, merely act as conditional carcinogens [594, 595 596] The "conditional carcinogenic" effect of sex hormones will however appear only if there is a special predisposition to cancer or "cancer taint" [765], This is understandable if it is recalled that sex hormones have a proliferative action on sexually differentiated tissue. This physiological action affects both normal cells and cells with a "predisposition to cancer." Only the administration of excessively high doses of hormone over pro-

longed periods, such as is never encountered therapeutically, could lead to the formation of malignant tumours, and this could happen only in a tissue already "predisposed to cancer" on the basis of other, multiple factors and noxious influences. Hence, sex hormones do not lead to cancer; if used in very large doses, they may simply contribute secondarily to its appearance in rare cases. The best known example is the rare finding of a breast carcinoma after oestrogen treatment of prostatic carcinoma [597]. Carcinogenic effects may be excluded with certainty as regards administration of therapeutic and therefore physiological doses. Physiologically justified, therapeutically necessary, and correctly dosed employment of sex hormones may therefore continue without anxiety [595].

Therapeutic Use of Desoxycorticosterone Acetate

Although even now there is no uniformity of views on all aspects of adrenal cortical function, opinion is unanimous as regards the great significance of the cortical hormones in healthy and diseased organisms. Treatment of certain diseases with Primocort (desoxycorticosterone acetate) has produced impressive results [2, 10, 153, 154 159, 177].

Addison's disease

Among the multiplicity of disturbances of adrenal cortical function known today, Addison's disease occupies the first place only in a historical sense, clinically it plays a very small part. The following are the symptoms: lack of energy, extreme fatiguability, dyspepsia, headaches, brown pigmentation of skin and mucous membranes, progressive loss of weight, hypoglycaemia, hypotension, anaemia, dehydration with thickening of the blood and rise in residual nitrogen, fall in salt content and rise in potassium content of the serum.

The typical clinical picture is rare. Aetiologically, tuberculosis of the adrenal cortex is commonest; rarer causes are syphilis, tumours or an adrenal cortical atrophy as a result of chronic infection. The increased excretion of water and of salt leads to dehydration of the tissues and concentration of blood during the course of the disease. The blood sugar level is normal or slightly lowered, the response to insulin enhanced, the glycogen content of the liver reduced, and the neogenesis of sugar from protein also reduced [204, 598].

The different views on the physiological actions and purposes of desoxycorticosterone are dealt with on page 64. Stasis of phosphorus in the adrenal cortex and the disturbances of the *necessary phosphorylation* processes in the whole organism associated with hypofunction, as well as the disappearance of phosphorus with hyperfunction, confirm the correctness of the phosphorylation theory mentioned on page 66 [599, 179]. Treatment of Addison's disease is aimed at the substitution of inadequate or completely absent hormones. Statistical studies extending over a period of 10 years have shown that the mortality before 1930 was 63% and after the introduction of desoxycorticosterone therapy was only 15.7%. These figures clearly show the advantage of treatment with Primocort (desoxycorticosterone acetate). The favourable action of desoxycorticosterone leads to subjective improvement, with disappearance of all symptoms, and to retention of salt and water, raised potassium excretion in the urine, restoration of normal sodium, chloride and potassium relations in the plasma and tissues, rise in blood pressure, gain in weight, general increase in strength and so on.

The hormone requirements of individual patients with Addison's disease is very variable. It is therefore always necessary to determine the substitution dose required. The therapeutic doses of Primocort necessary vary between 5 mg. and 40 mg. intramuscularly daily [600]. Supplementation by giving large doses of salt, and limitation of potassium intake, are now considered to be a mistake, since it has been shown that the combination of desoxycorticosterone with a high-sodium and low-potassium diet entails not inconsiderable risks [201, 205, 601, 602]. On the other hand, a diet high in sodium and chloride and poor in potassium helps hormone therapy (cf. page 74). In the treatment of Addison's disease hormone therapy and diet should mutually supplement and aid each other.

These relationships should be carefully determined in each case, such determination ensuring an optimum result. If adrenal cor-

tical tuberculosis is present, this must naturally be treated like any other organ tuberculosis, in addition to desoxycorticosterone therapy.

For maintenance treatment, Primocort implants have been specially used recently [603, 604, 605, 598]. The simultaneous introduction of three 100 mg. implants of Primocort usually keeps the organism in balance for 3 to 6 months. This technique ensures an even supply of hormone to the body, and makes the patient and the physician independent of daily injections. Before treating Addison's disease with implants, the patient's actual daily requirements for hormone must be determined by using intramuscular injections for at least 4 to 6 weeks. The amount of hormone to be implanted depends on the optimum dose to which the patient has been adjusted. Before repeating an implantation, the then requirements of hormone must also be freshly determined by a new series of injections. The period between the diminution of effect of an implant and the complete absorption of the compressed substance is probably fairly long. As soon as loss of weight, deterioration in general condition, and fall in blood pressure suggest a diminution in effect of the implant, supplementary injections of Primocort should be given intramuscularly immediately. At the earliest, a fresh implantation is indicated at the end of two months, since by this time it is unlikely that large fragments of implant remain; in conjunction with injections, the latter might result in overdosage.

Minor adrenal cortical insufficiency (Addisonism)

Less marked degrees of adrenal cortical insufficiency (the so-called Addisonism) are less well known but widespread Partial failure of adrenal cortical function is shown by rapid fatigue, headache, loss of weight, a low blood pressure and low blood sugar, tendency to subnormal temperatures, slowing of the pulse and circulatory weakness. In the blood and tissues the same changes are found as in Addison's disease, but are less marked

The condition is often of constitutional origin, and may be familial [606]. It may be secondary to infections. Serial evaluation of the lowered blood pressure and blood sugar values and of the sugar tolerance curves are of diagnostic and prognostic significance. In order to determine a substitution dose, treatment should begin with a normal diet and daily injections of 5 mg. Primocort intramuscularly, or with daily buccal administration of three or four 1 mg. tablets. *Improvement, which sets in during the first few days, is then the yardstick for further dosage* (cf. page 223).

Adrenal cortical hyperfunction (Interrenalism)

In contrast to the above disturbances, hyperfunction of the adrenal cortex may be produced by overproduction of adrenocorticotropic hormone (ACTH) in the anterior pituitary or by adenomatous growth of cortical substance, or occasionally by hypernephroma. These neoplasms may be benign or malignant. In children, there is an acceleration of physical development, including the genitals, with premature appearance of secondary sex characters, and in girls an extraordinarily pronounced growth of the clitoris (precocious puberty). This puberty outstripping normal development, and so-called intersexuality (pseudohermaphroditism), are expressions of adrenal cortical hyperfunction. In girls, male sex characters appear (hirsutism: increased hair growth on the face and body) If an adrenal cortical tumour is present, treatment must begin with the operative removal of the tumour. After this it may be necessary to give substitution therapy with desoxycorticosterone for some time If the disease appears at a later date, that is, after puberty, there is also disturbance of sexual nature, with reversal of sex characters.

In differential diagnosis, it is necessary to clarify the point whether the interrenalism may be the result of disease of the pineal or of gonadal tumour (testicular or ovarian type [607]). The prognosis is then usually unfavourable.

Cushing's syndrome

Cushing's syndrome is another severe disease syndrome which may be due either to tumour of the adrenal cortex or tumour of the pituitary. Adenomatous growths of the adrenal cortex or basophil adenomata of the pituitary lead to a very characteristic clinical picture: rapidly increasing deposition of fat, sometimes painful, on the back of the neck and the body but not on the limbs, osteoporosis, increase in erythrocyte count, hypertension, hypercholesterinaemia, reddish-blue striae on the skin of the abdomen, and gonadal disturbances. These are in some cases associated with diabetes mellitus, and a tendency to bleeding into the skin, the genitals and the lungs

The differential diagnosis usually presents considerable difficulty [608]. Determination of ketosteroid excretion may often lead to clarification (cf. page 63). If a tumour of the adrenal cortex is present, the latter should be removed operatively, substitution therapy with desoxycorticosterone is then carried out. In cases of basophil adenoma of the pituitary, X-ray or radium irradiation or operation is indicated. Improvement in signs and symptoms is also sometimes obtained with large doses of oestrogen (10—20 mg. Progynon B oleosum forte intramuscularly daily) [609].

A case has recently been described of clitoris hypertrophy with pituitary dwarfism and degeneration of the hip-joint probably of endocrine origin, in which complete cure was obtained by years of oestrogen treatment [610]. The results of treatment suggest that a pituitary tumour was present, in which the oestrogens inhibited the activity of the basophil cells of the anterior pituitary

Chronic joint diseases

Adrenal cortical hormones have recently attracted widespread interest because of the controversy over the treatment of chronic

joint disease. A definitive assessment of hormone therapy in these conditions is unlikely to be obtainable in the near future Experimental studies, theoretical considerations and clinical experience showed that compound E (cortisone) would lead to therapeutic results in acute rheumatism, rheumatoid arthritis and other joint diseases. Since the chemical structure of cortisone differs only a little from that of desoxycorticosterone, it seemed logical to try out Primocort in these conditions, especially as the synthesis of cortisone at first presented considerable material and financial difficulties.

Treatment with desoxycorticosterone acetate combined with vitamin C, first carried out in Sweden and later in Anglo-American circles, led to favourable results in certain disorders of joints. Experience so far shows that side-effects need not be feared. In contrast to cortisone treatment, the dosage of Primocort used corresponds to that employed elsewhere in hormone therapy.

These good results were to a large extent confirmed in Germany [189, 190, 191, 192, 611, 612, 613]. According to experience so far, the primary chronic, non-inflammatory, degenerative forms of many disorders of joints of very varied aetiology appear to respond best to combined therapy with Primocort and ascorbic acid. Some excellent results have been recorded in conjunction with physiotherapy. If a joint disorder is going to respond to this therapy, improvement usually sets in after the second or third injection, and can usually be maintained in such a case by further combined injections. The original suggestion has apparently been confirmed that the prospects of success in treatment depend to a great extent on the choice of chronic degenerative deforming conditions, as opposed to acute inflammatory cases. With treatment not only does pain disappear, but also there is considerable improvement in function, if the treatment is combined with the usual physiotherapeutic measures, which should not be neglected in any case.

Experience has shown that treatment must be carried out strictly according to the following technique. An intramuscular injection of 5 mg. Primocort is first given, followed immediately – at the longest within 5 minutes – by intravenous injection of 1 g. ascorbic acid (vitamin C). Both agents may also be injected intramuscularly together in the same syringe (see page 249). To simplify the injection technique, the 5 mg. of Primocort may also be employed intravenously, simultaneously with the ascorbic acid. The explanation of the biochemical processes taking place in the organism after this treatment has not yet been given in full; further research is necessary.

Infective-toxic diseases

Recently, increasing importance has been attached to the concept of relative adrenal cortical deficiency, possibly in connexion with a dysfunction of the pituitary, in infective or toxic processes [181 614, 615 157, 181 186].

According to clinical experience so far, desoxycorticosterone treatment should be considered in a great number of infectious diseases, especially diphtheria, scarlet fever, bacillary dysentery, typhoid fever and tuberculosis. In these conditions, pathological changes are demonstrable in the adrenal cortex. The clinical features of these diseases are also often suggestive of involvement of the adrenal cortex Proof has been advanced that animals with diphtheria intoxication can be kept alive in a relatively high percentage of cases by use of desoxycorticosterone acetate [616] The observation that patients with Addison's disease often undergo a dangerous crisis as a result of trivial infection, and the endocrine-physiological relationships (cf. pages 65 and 71), together with a great deal of other experience, definitely indicates the significance of adrenal cortical hormone in infections and intoxications. Attention has recently *again been drawn to* the connexion between the pituitary, the adrenal cortex and the intoxications [181 156, 157]. Desoxycorticosterone increases the

resistance of the organism to infections, and assists the body to combat intoxications. It is generally sufficient to give 5 mg. intramuscularly 2 or 3 times a week, and one 1 mg. tablet buccally 3 times a day. To accelerate convalescence, 2 or 3 tablets are given buccally daily.

Dosage must be individually adapted to the diseased organism *It is of importance in assessing dosage to remember that clinical* experience has shown that hormone requirements are significantly greater in infections and physical stress than in physiological conditions.

Encouraging results have been obtained in tuberculosis by supplementary treatment with desoxycorticosterone. The patients' general condition and physical resistance improved surprisingly in some cases under this therapy [196, 617, 618, 619, 620, 621, 766].

Coeliac disease and the common intoxications of childhood of endogenous and exogenous origin respond excellently to desoxycorticosterone administration, with return of fat and carbohydrate absorption to normal and prevention of further dehydration [120].

"Non-specific" intoxications are also favourably influenced by administration of desoxycorticosterone. Such intoxications are the results of burns, scalds, radium, X-ray and ultraviolet irradiation, and may be interpreted as damage to the adrenal cortex as a result of increased stress due to products of protein degradation [622, 623]. In severe cases, 5 mg Primocort is given every two or four hours intramuscularly; in other cases, 2 injections a week, each of 5 or 10 mg., are often sufficient. Prophylactically before irradiation with radium, X-rays or ultraviolet light 2.5 mg is given half an hour previously intramuscularly, or two 1 mg. tablets buccally.

For treatment of the so-called "radiation sickness" a dosage of one tablet Primocort buccally 3 or 4 times a day is recommended

Vomiting and hyperemesis of pregnancy

It has now been shown that an essential factor in vomiting and hyperemesis of pregnancy is an adrenal cortical insufficiency due to pregnancy. Carbohydrate utilization in the body is thus diminished. Liver and musculature become depleted of glycogen, and as a result of defective ketolysis ketone bodies accumulate in the blood. Desoxycorticosterone therapy overcomes these substantial disturbances of metabolism, which are often the cause of the symptoms, and thus relieves the clinical symptoms. In cases of mild and moderate severity, the daily administration of 1 to 3 tablets of Primocort buccally often leads to the disappearance of all manifestations. It is advisable to continue buccal treatment with Primocort tablets for a while even after the cessation of vomiting. In cases of severe hyperemesis, treatment must be carried out with 5—10 *mg.* Primocort intramuscularly daily or several times a week (cf. page 157).

Liver protection

During the last decade, adrenal cortical hormone has become of increasing importance in the treatment of diseases of the liver and biliary tract [767]. The detoxicating action of desoxycorticosterone in relation to hepatotoxic substances, the capacity of desoxycorticosterone to diminish blood volume in partially hepatectomized animals, and the stimulation of the glycogen-forming function of the liver by desoxycorticosterone led to its employment in liver damage (infective hepatitis, catarrhal icterus, subacute and acute yellow atrophy of the liver, cirrhosis of the liver, cholangitis, cholecystitis and cholelithiasis with secondary liver damage) Adrenal cortical hormone always exerts a glycogen-forming effect, independent of the height of the blood sugar level [157, 624, 625, 626] In diseases of the liver parenchyme, desoxycorticosterone exercises a controlling action on the disturbances of mineral balance and glycogen anabolism.

In hepatitis, there is a change in cell permeability with penetration of sodium and chlorides into the liver cells, and simul-

taneous displacement of potassium and phosphorus ions. Through this disturbance of *mineral metabolism, the balance between* potassium and sodium in the tissues is displaced in favour of sodium. *This results in oedema, dilatation of lymph vessels, and* serous inflammation of the liver parenchyma. By means of *adrenal cortical hormone, physiological electrolyte balance and* the normal permeability of the liver cells can be restored [625, 627, 628, 629].

In many types of liver damage, the cells of the liver parenchyma *are depleted of* glycogen. *Liver cells* poor in glycogen lose *their* detoxicating properties to a great extent, and cannot combat *toxic injuries to the organism nearly so effectively as liver cells* rich in glycogen. Desoxycorticosterone administration also *increases the glycogen content of the damaged liver cell* [630, 631]. Recognition of these relationships affords a firm basis for the *use of desoxycorticosterone in diseases of the liver and biliary* tract.

As well as a diet poor in fat and protein, patients with hepatitis should be given 5—10 mg. of *Primocort intramuscularly daily, in latent icteric and chronic forms of liver damage with a raised* bilirubin level in the serum, 10 mg. *of Primocort* should be given *intramuscularly twice a week.*

Acute hepatitis which has been overcome but not cured, and *threatens to become chronic, shows significant improvement after* implantation of desoxycorticosterone acetate [632]. *By its use,* re*covery of that part of the liver parenchyma still capable of* function is promoted, and cirrhotic changes in the periportal *tissue are to a great extent arrested* [767].

In severe chronic cholangitis with secondary damage to the liver *parenchyma, implantation of a total of 400 mg Primocort led to* complete cure [633].

In cases of chronic liver disease, sugar excretion in the urine during galactose and *laevulose tolerance tests diminishes with adrenal cortical hormone therapy,* as does the pathological

hyperglycaemia; this is a proof of the assimilatory effect of desoxycorticosterone acetate on carbohydrate metabolism In animal experiments, liver damage due to phosphorus or alcohol intoxication can be overcome with large doses of adrenal cortical hormone, as can the hyperindicanaemia typical of such damage [634]. In cases of chronic disease of the gall-bladder, which may have persisted for years, the constant pain in the liver region particularly tends to disappear during desoxycorticosterone treatment [635]. With doses of 10 mg Primocort intramuscularly twice a week, there is often a sudden disappearance of colic. The irritability and increase in tonus of the gall-bladder musculature are diminished and even completely overcome [45, 26, 636, 637, 627, 755, 756]. In these cases, at least 10 or 12 intramuscular injections of 10 mg. Primocort are needed for a satisfactory result. When a result appears, the dose of Primocort may be gradually reduced According to recent studies, desoxycorticosterone therapy gives equally rapid and significant results when there are symptoms of recurrence after gall-bladder operations [635].

For the treatment of milder cases of catarrhal jaundice and gall-bladder disease, for the after-treatment of infective hepatitis, toxic damage to the liver, and cholangitis, and for the prevention of gradual possible development of liver cirrhosis after diseases of the liver and biliary tract, one tablet of Primocort (1 mg.) should be given buccally 2—4 times a day for several weeks.

Vegetative dystonia (autonomic imbalance)

The adrenal cortex also plays an essential part in the regulation of blood volume, blood pressure and capillary tonus. This tendency to cause stabilization of the circulation is also of value in cases of low blood pressure and hypotensive states during convalescence.

The connexions between adrenal cortical function and vegetative dystonia have recently received particular attention. Desoxycorticosterone is of great importance for the control of the cir-

culation, and the latter is extremely unbalanced in patients with vegetative dystonia. The hormone also plays an essential part in the tonus of the autonomic nervous system indirectly by its effect on electrolyte balance [207, 208, 209, 210]. The mechanisms of adaptation to special stresses are disturbed in patients with vegetative dystonia, and in many cases there is a marked tendency to low blood pressure. Tests of adrenal cortical function in patients with vegetative dystonia have revealed significant deviations from the normal; such deviations may be taken as proof of the presence of an adrenal cortical insufficiency. In particular, those types of vegetative dystonia which respond poorly to sedation show obvious improvement on administration of desoxycorticosterone, possibly in combination with vitamin C [209]. Primocort tablets are particularly suitable for compensating for dysregulation of adrenal cortical origin in vegetative dystonia, because they afford a means of ensuring a small and continuous supply of hormone. It is advisable to give 1—3 tablets of Primocort buccally daily over a period of 4—8 weeks.

Gastric and duodenal ulcer

Adrenal cortical hormone can also produce very good results in the treatment of gastric and duodenal ulcer. Pathological studies have shown that a normal function of the adrenal cortex is essential for maintenance of a physiological condition of the mucosa of the digestive tract [638, 639]. With desoxycorticosterone therapy, there is a remarkably rapid disappearance of pain in gastric and duodenal ulcer, even in some cases in which the usual therapeutic measures have been unsuccessful [610]. In a high proportion of cases, even advanced ulcers heal completely, and the tendency to recurrence is lowered. Even in the case of ambulant patients continuing to work and having no other forms of treatment, good results have been reported from adrenal cortical hormone therapy [611, 612, 613, 614, 615]. The good results of desoxycorticosterone therapy in peptic ulcer

can be explained on the properties of the hormone to lower capillary permeability [646] and counter inflammation [647], and on its ability to promote circulation in the mucosa [648] and destroy histamine [649, 650]. In severe cases, 10—20 mg of Primocort is injected intramuscularly daily or every other day to a total of about 150—300 mg. In milder cases, and for the prevention of recurrence, 1 Primocort tablet buccally 2—3 times a day is indicated (cf. Treatment with Sex Hormones, page 180).

Skin diseases

Desoxycorticosterone has a favourable influence on a variety of skin disorders The most important of these are acne vulgaris, rosacea and rosacea keratitis, as well as psoriasis, especially psoriatic arthropathy.

If desoxycorticosterone therapy is carried out systematically in cases of acne vulgaris, if necessary with administration of the sex-specific sex hormone, complete cure may be obtained in the majority of cases [651, 652]. The present view of the pathology of rosacea is that disturbances of function of liver and gastrointestinal tract play a part, as well as hormone deficiency, in particular of the adrenal cortex and gonads, together with disturbances in the autonomic nervous system.

The most important factors in this disease are considered to be the constitutional lability of the neuro-vascular system in the facial area, and the dysfunction as regards liver metabolism. Desoxycorticosterone therefore offers real opportunities for causal therapy, since it has a direct or indirect controlling action on all these disturbances [651, 653].

Ophthalmologists have repeatedly confirmed the excellent therapeutic effect of desoxycorticosterone acetate in rosacea keratitis and conjunctivitis [654, 655, 656].

Many authors now support the view that adrenal hypofunction plays a significant part in the aetiological complex of psoriasis [657, 658, 659] Particularly good therapeutic results can be ob-

tained in psoriasis by combining desoxycorticosterone therapy with administration of small doses of vitamin C. The diet should be poor in potassium [660].

The dosage to be considered in all skin disorders is 5—10 mg. Primocort intramuscularly 2 or 3 times a week; in mild cases requiring long-term therapy, 1 tablet of Primocort should be given buccally 2 or 3 times a day. During hormone therapy, the usual local treatment should naturally not be neglected.

Further indications

Finally, desoxycorticosterone has also been employed in surgical shock [180], in excessive thinness [661], in the care of premature infants, and also in diabetes mellitus because of its insulin-sparing effect [662, 663]. If the pituitary is involved in excessive loss of weight (e. g. in Simmonds's cachexia), desoxycorticosterone should be administered in combination with anterior pituitary hormones ([603, 664]; cf. page 201). *The question of treatment of this pituitary disorder with ACTH is discussed on page 201, and* with Primothyron on page 217.

Therapeutic Use of Tropic Hormones of the Anterior Pituitary

The Gonadotropic Hormones

The absence of synthetic preparations, and the difficulties already mentioned of obtaining gonadotropic hormones from the pituitary, have limited us to the employment of serum and chorionic gonadotropins· Priantin and Primogonyl. As described earlier, Priantin corresponds in its biological effect to follicle-stimulating hormone, and Primogonyl to the luteinizing hor*mone of the anterior pituitary* [716].

Sterility

Sterility in *the female* and in the male is often the result of inadequate formation of gonadotropic hormones in the anterior pituitary, their stimulating effects on the ovaries and the testes being then insufficient. The folliculotropic factor of the anterior pituitary stimulates the beginning of growth of the primary follicle in women, and promotes the growth of the follicle, but cannot by itself provoke ovulation.

In the male, the spermatogenetic (folliculotropic) factor of the anterior pituitary stimulates the germinal epithelium of the testes, and promotes the new formation and maturation of spermatozoa [717 718].

Hence, sterility depending in the female on absence of follicular maturation and ovulation, and in the male on azoospermia and failure of maturation of the germinal cells, responds well to

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Eunuchoidism

The subjects of eunuchoidism of *pituitary* origin can usually be recognized by their abnormal height and good covering of fat. The genitals are small, and libido and potency are often subnormal. There is sometimes a concomitant bilateral cryptorchidism. The clinical picture is not always easy to differentiate from that of adiposo-genital dystrophy. An important point in the history is often the time of onset of the disease, which is as a rule already recognizable between the 10th and 12th years. Body growth may also be retarded (dwarfism). The cerebral signs and symptoms present in dystrophia adiposo-genitalis (headache, vertigo, signs of increased intracranial pressure, optic atrophy) are absent in eunuchoidism.

In so-called *late eunuchoidism* physical development is already ended and secondary sex characters have already appeared before the onset of a disturbance of gonadal function with all its concomitants regression of secondary sex characters and development of the typical eunuchoid fatty covering. For suggestions for therapy, see under Simmonds's cachexia.

Simmonds's cachexia

Simmonds's cachexia is the result of a high-grade atrophy of the anterior pituitary, and manifests itself as an atrophy of the internal organs, extreme loss of weight, disturbances of metabolism, fall in basal metabolism and finally complete mental and physical decay. The disease affects both sexes, and is not infrequently described in women after a delivery [722, 723, 724]. In the latter cases it may in rare instances be due to a total necrosis of pituitary (Sheehan's disease) [725]. In the treatment of this condition, a trial may be made of either ACTH (cf. page 216), thyrotropic hormone (cf. page 217), or the gonadotropic factors, as well as adrenal cortical hormones, since many of the symptoms suggest an insufficiency of the adrenal cortex.

administration of serum gonadotropin, which primarily contains the folliculotropic factor. In necrospermia, it is advisable to combine this with the male sex hormone testosterone. If sterility in the female is due to absence of ovulation (cf. basal temperature measurement on page 146), a course of Priantin during the first 14 days of the cycle, *followed up by the luteinizing Primogonyl* is indicated ([719, 720]: for dosage cf. page 267). In sterility associated with a shortened secretory phase, treatment with *Primogonyl alone is indicated, 500 i. u.* being given intramuscularly every other day after ovulation until the period begins ([721]). If the uterus is hypoplastic, pre-treatment with oestrogens is advisable.

In the male, serum gonadotropin promotes the growth of the seminal epithelium. Two or three ampoules of Priantin, each of 5,000 i. u. should be injected i. m. every week. Treatment should consist of series of 10 injections with interpolation of rests of several weeks. If the patient does not respond sufficiently, a combination with testosterone treatment is advised (cf. pages 168/169).

Impotence

The difficulty of treatment of impotence has already been discussed on page 167. If the impotence is the consequence of an endocrine disturbance, in addition to testosterone treatment a trial of chorionic gonadotropin therapy should be made. The latter chiefly contains the interstitial-cell-stimulating factor of the anterior pituitary, and thus acts upon the interstitial tissue of the testis. Stimulation of the testis brings about an increase in output of testosterone. This frequently leads to restoration of the testis to complete function. There is a simultaneous improvement in mental and physical efficiency, such as occurs with testosterone treatment of the male climacteric. A total of about 20—30 injections of Primogonyl should be given, 300 to 1,000 *i. u. being* injected 1—3 times a week intramuscularly.

Dystrophia adiposo-genitalis

Primogonyl treatment of this disease, which principally occurs in males, may often lead within a few weeks to return to normal of fat distribution in men or boys, and development of the genitals. According to the patient's age, one to three injections of 300 to 1,000 i. u. Primogonyl are given intramuscularly every week. When improvement appears, the dose of 300 i. u. may be maintained, or a previous higher dose may be lowered to this level.

Amenorrhoea

Treatment of primary amenorrhoea due to hypogenitalism and follicular immaturity with serum gonadotropin is of great importance. Serum gonadotropin chiefly contains the follicle-stimulating factor of the anterior pituitary, and thus leads to stimulation of ovarian functions so that maturation of the follicle may be completed.

The effects of serum gonadotropin naturally suggest its use in secondary amenorrhoea as well The type of amenorrhoea which follows a delivery is particularly suitable, because it is often associated with pituitary hypofunction [733]. The ovaries must however be capable of some function if treatment is to be successful As a result of the stimulation due to serum gonadotropin the ovaries may again become capable of causing proliferation of the endometrium and its transformation into a secretory phase [728, 729, 730, 731].

In amenorrhoea, one ampoule of 1,000 or 5,000 i. u. Priantin should be given intramuscularly 2 or 3 times a week. After two weeks of Priantin treatment, timed in accordance with the menstrual cycle, an interval of 14 days should be interpolated. Before the period, a supplement of Proluton, 5—10 mg. i. m., should then be given [732, 733].

Metropathia haemorrhagica cystica

Gonadotropins have proved valuable in the treatment of cystic glandular hyperplasia of the endometrium. The results are ex-

The result depends on the degree of pituitary insufficiency. The following therapeutic suggestions have proved of value in both the conditions described above:

Simmonds's cachexia in w o m e n is treated with Priantin, with due regards to the menstrual cyrle. In the first two weeks of the cycle, one ampoule containing 5,000 or 1,000 i. u. is given intramuscularly *2 or 3 times a week. Treatment is resumed* after the menstrual period or after a 14-day interval.

In m e n suffering from eunuchoidism and Simmonds's cachexia series of 10 injections are given with interpolation of intervals of several weeks; in each series 2—3 ampoules of 5,000 or 1,000 i. u. Priantin are given i. m. weekly. Combination with testosterone has often proved of value. The procedure for a therapeutic trial of thyrotropic hormone of ACTH is described in detail in the relevant sections of the Suggestions for Dosage on pages 265 and 266

In Simmonds's cachexia in both sexes supplementary desoxycorticosterone treatment is recommended, possibly by implantation of the hormone. This treatment presents a difficult problem to the doctor, and must be carefully adapted to the individual case. Implantation of calf pituitary, which has frequently been advised, can only give short-term results [726, 727] (cf. page 104).

Cryptorchidism

Bilateral cryptorchidism can often be overcome without operation by giving Primogonyl. This diminishes the contractility of the vas deferens and thus assists the descent of the retained testis. The optimal age for treatment lies between the 10th and 12th years. Treatment must continue for 4—6 months, according to the case. According to the child's age, one or two injections of 300—1,000 i. u. of Primogonyl are given intramuscularly weekly. Simultaneous administration of small doses of testosterone may accelerate the result.

diseases of very varied aetiology corresponds closely to the group described by Selye as diseases of adaptation (183, 184) (cf. page 66). It is beyond the scope of this monograph to describe in detail the therapeutic effects of ACTH in every disorder in which the hormone might be useful. Details of ACTH therapy in individual indications must be sought in the review articles (285, 316, 317, 187, 750), the brochure ACTH "Schering A. G. Berlin," and the special literature on ACTH treatment of certain diseases. According to the present state of research, diseases may be classified as follows in relation to the possibility of employment of ACTH therapeutically*:

1. Diseases in which the therapeutic effect of ACTH has been proved:

   Acute rheumatism, especially with rheumatic cardiac complications
   Primary and secondary rheumatoid arthritis
   Acute gout
   Disseminated lupus erythematosus, especially the acute form
   Status asthmaticus and severe bronchial asthma
   Periarteritis nodosa
   Ulcerative colitis
   Severe allergic disorders (serum sickness, vasomotor rhinitis, urticaria, sensitivity to drugs, allergic dermatitis)
   Eczema
   Exfoliative dermatitis
   Erythema multiforme
   Dermatomyositis
   Neurodermatitis
   Psoriasis, especially psoriatic arthropathy
   Pemphigus
   Herpes zoster

* In the section on Therapy and Suggestions for Dosage (see page 220) only those diseases are dealt with in which the effect of ACTH treatment is certain

plicable of the basis of the mechanism of action described in the physiological and pharmacological sections.

On alternate days for 10—14 days 1,000 i. u. Primogonyl are given i. m. If treatment is carried out with progesterone, the supplementary use of Primogonyl, in 3,000 i. u. doses on 3 successive days every 10 days i. m., is advised in order to prevent recurrence.

Adrenocorticotropic Hormone (ACTH)

The therapeutic effects of adrenocorticotropic hormone (ACTH) are in general identical with those of cortisone, since ACTH itself cannot develop a curative action. Its effects depend upon the fact that it stimulates the adrenal cortex to secrete 11-oxycorticoids. Provided that the adrenal cortex is capable of function, ACTH therapy always leads to increased activity of this organ This is shown anatomically by the hypertrophy of the organ. A clinically utilizable measure of the response of the organism to ACTH therapy is the significant rise in excretion of 17-ketosteroids and 11-oxycorticoids in the urine [106, 107, 173, 174] (cf. page 90). *If however cortisone is administered in conditions suitable for ACTH medication, production in the anterior pituitary and output of ACTH are inhibited Hence prolonged administration of cortisone leads to hypofunction and atrophy of the adrenal cortex, clinically demonstrable as a diminution in excretion of 17-ketosteroids and 11-oxycorticoids. This danger need not be feared with ACTH administration.*

The therapeutic employment of ACTH is indicated in all those conditions in which a general inhibition of excessive mesenchymal reactions must be achieved. The prospect of successful ACTH treatment is greater, the less differentiated the mesenchymal tissue which the ACTH is intended to modify [350, 351, 187]. In the American literature, a multiplicity of diseases in which ACTH may be of therapeutic value is grouped together under the name of the mesenchymoses or collagen diseases [705]. This group of

Progressive muscular dystrophy
Glomerulonephritis (especially on an allergic basis)
Liver disorders (hepatitis and cirrhosis of the liver)
Thromboangiitis obliterans (Buerger's disease)
Osteoarthritis
Paget's disease
Pernicious anaemia
Keloid
Central anoxaemia

4. Diseases in which ACTH therapy has proved useless:

Amyotrophic lateral sclerosis
Carcinoma (possible favourable effect on general condition, no effect on the malignant tumour itself)
Poliomyelitis
Sarcoidosis
Herpes simplex
Cystic fibrosis of the pancreas

5. Contraindications to use of ACTH:

Tuberculosis
Diabetes mellitus
Cushing's syndrome
Osteoporosis and osteomalacia
Severe cardiac insufficiency with decompensation
Acne vulgaris
Hirsutism
High-grade hypertension (especially fixed high blood pressure)
Inflammations of the kidneys
Acute lesions of the peritoneal cavity (peritonitis, fresh gastric and duodenal ulcer)
Septicaemia
Severe psychopathies and psychoses
Extensive wounds in process of healing

Panhypopituitarism (total pituitary insufficiency)
Allergic and inflammatory diseases of the eye (blepharitis, chorioiditis, spring conjunctivitis, iritis, iridocyclitis, keratitis, central retinitis and retinitis pigmentosa, scleritis, sympathetic ophthalmia, uveitis)
Retrobulbar neuritis
Nephrotic syndrome
Acquired haemolytic jaundice
Idiopathic hypoglycaemia
Eosinophilic lung infiltrate (Loeffler's syndrome)
Very severe burns
Anorexia nervosa

2. Diseases in which a therapeutic effect of ACTH is possible:

Agranulocytosis
Thrombopenic purpura
Systemic malignant disease (acute leukaemias, chronic lymphatic leukaemia, Hodgkin's disease, multiple myeloma, lymphosarcoma)
Boeck's sarcoid
Multiple (disseminated) sclerosis
Necrotizing enteritis
Trichinosis
Alcoholism
Pneumonia (especially *fibroblastic pneumonia in berylliosis*)
Hyperemesis gravidarum
Premature and frail newborn infants

3. Conditions in which the therapeutic effect of ACTH is questionable:

Scleroderma
Glaucoma
Malignant exophthalmus
Myasthenia gravis

antibodies have been found in the blood [290]. In many disorders, the therapeutic effect of ACTH is more lasting than that of cortisone. This fact is probably explicable on the grounds that, in contrast to cortisone, ACTH causes a hypertrophy particularly affecting the middle cortical layer or zona fasciculata, which is the site of production of glucocorticoids. As a result the output of 11-oxycorticoids is still increased for a time after the administration of ACTH has ceased.

Most of the side-effects which may appear during treatment with this high-potency hormone are not toxic effects but merely the consequence of the pharmacological actions of ACTH [303, 707, 708, 709, 710]. After ACTH therapy ceases, all the side-effects very rapidly disappear. Side-effects are more common in women, particularly at the climacteric, and in children than in men. They generally appear only if treatment is given for a short time with very large doses or for months with smaller doses. In the early days of the employment of ACTH about 25% of all patients treated showed marked side-effects, whereas nowadays the percentage has fallen to about 8%, chiefly as a result of the lower dosage now used and the greater purity of modern ACTH preparations. At the beginning of a course of ACTH there is usually a definite euphoria, which may amount to a hypomanic state with very large doses [373]. As treatment proceeds, and particularly after the hormone has been discontinued, this euphoric state gives place at times to a marked depression [711]. With continued ACTH treatment, there may appear a syndrome resembling Cushing's syndrome associated with rounding of the face (moon-face), increase in bodily circumference, acne, hirsutism, striae distensae, and occasionally oedema of the legs. In the case of menopausal patients, who are more prone to develop a Cushing syndrome than other patients, the danger may be prevented by supplementary administration of 5 mg. oestradiol benzoate intramuscularly twice a week [285]. To combat the increased nitrogen loss during ACTH medication, in addition to

Fresh fractures
Addison's disease
High-grade adrenal cortical insufficiency (due to local damage to the adrenal cortex)

In using ACTH therapeutically, the physician must always bear in mind that this high-potency hormone has a profound influence o n a l l metabolic processes in the organism. In the present state of research, the requirement must still be laid down, that ACTH treatment is o n l y to be carried out i n h o s p i t a l under the constant check of all essential laboratory tests (see page 90). ACTH treatment must never be regarded as routine therapy to be carried out according to a schedule without knowledge of the *manifold effects of this hormone. In any indication, ambulant* treatment is therefore totally unjustified.

Because of the intense activation of protein metabolism, the diet during a course of ACTH should be as rich in protein as possible, but poor in salt and water. Because ACTH leads to increased excretion of potassium, care should be taken that the diet is rich in potassium. With high dosage, it is advisable to administer 2—5 g. potassium chloride daily by mouth. Large doses of vitamin C may significantly enhance the effect of ACTH, and simultaneously protect the adrenal cortex against depletion in the vitamin.

ACTH has a general antipyretic and analgetic action. This fact should always be borne in mind during treatment. Fall in temperature and relief of pain during ACTH treatment should not always be considered as evidence of a direct favourable effect on the disease process as such [705] When ACTH therapy has continued for a very long time, many patients in spite of an initial good result cease to respond to the hormone, because antihormones have formed in the organism and led to development *of a refractory state to ACTH. In animal experiments,* after prolonged administration of large doses of ACTH specific

unrecognized [715]. The danger of masking of symptoms by ACTH treatment must always be remembered during ACTH treatment. Because of inhibition of fibroblast proliferation, and also of regeneration of cartilage and bone by ACTH, poor healing of fresh wounds and fractures may be observed, as well as considerable delay in scar formation during treatment with this hormone [356].

The dosage level of ACTH always depends on the nature and the severity of the disease under treatment; apart from this, the optimal dose also varies very much with the individual. So far the best modes of administration have proved to be intramuscular injection and intravenous drip infusion in 5% glucose solution. Intravenous injection is decidedly inadvisable on account of the greater risk of acute side-effects and the much poorer utilization of the hormone due to its rapid excretion. As a general guideline to dosage in any case treated by ACTH, it is well to begin with a few days of more or less high initial dosage (between about 40 and 80 i. u.) and then to attempt, by continuous lowering of the daily dose, to determine the smallest dose still effective and to continue with the latter. Towards the end of a course of treatment, it is advisable to taper off very gradually with very small daily doses. In no circumstances should there be large gaps between the dose level on one day and the next. In treatment with large and moderate doses it is always necessary to fractionate the dose by dividing the daily amount into several equal single doses given every four, six or eight hours. Apart from very small doses given during tapering off, the daily quantity should never be given in a single dose, because the therapeutic effect is so much less on account of the low half-value time of ACTH in the organism (only about 3—4 hours). Gradual decrease in dosage during a course of ACTH is best carried out by lowering the individual doses on the one hand and increasing the intervals between the injections on the other. For details of ACTH dosage in various indications, the relevant

a high-protein diet, administration of testosterone propionate in 25 mg. doses 3 times a week has proved of value [285]. As regards sexual function, side-effects include transient diminution in libido and potency, irregularities of the menstrual cycle and amenorrhoea, especially in younger patients. Ovarian function is probably more easily disturbed in younger women by ACTH than in older ones. With patients in the climacteric, deficiency signs already present are usually intensified by ACTH treatment.

Other side-effects of ACTH medication are however of a more severe nature, and merit special attention in any course of treatment. With very high doses, there may be considerable retention of water and salt with associated risk of circulatory failure, especially if heart failure is present; in certain circumstances acute oedema of the lung and ascites may appear. If in spite of the contraindication which diabetes mellitus presents to ACTH therapy it becomes necessary to give the hormone to a diabetic already stabilized on a certain dose of insulin, hyperglycaemic shock may develop as a result of the lowering of carbohydrate tolerance. For this reason, diabetics must be given a significantly higher dose of insulin immediately on beginning a course of ACTH Occasionally a latent diabetes may be made manifest by ACTH [285]. Dangerous hyperglycaemia and glycosuria appear relatively seldom; they can be rapidly overcome by giving insulin. Changes in the electrocardiogram, muscular weakness, and temporary states of exhaustion during a course of ACTH are signs of a marked potassium depletion of the body. Such signs can be easily made to disappear by giving potassium chloride, as mentioned above. It is very important to recognize that ACTH lowers the resistance of the body to infection [712, 713]. As a result, acute lesions, particularly intraperitoneal ones, are masked by the effect of the hormone [714]. Thus during a course of ACTH perforation of an ulcer, or development of a peritonitis or acute appendicitis, may occur without abdominal-wall resistance, fever or pain, and hence remain completely

are now used diagnostically and therapeutically with the aid of radio-iodine. In the assessment of thyroid function with I^{131} and the treatment of thyroid tumours with radio-iodine, the employment of thyrotropic hormone is extremely valuable.

1. Assessment of thyroid function with Primothyron

The iodine content of the thyroid gland is to a large extent dependent on its functional state [665, 666, 667]. In the study of various thyroid disorders the administration of iodine isotopes has proved of great value in the elucidation of problems [668, 669, 670, 671, 672]. As little as 20 minutes after the intake of radio-iodine, its presence is demonstrable in the thyroid gland [669]. Normally about 50—60% of the radio-iodine is again excreted in the urine during the first 24 hours, whereas at the most 35% of the dose is still present in the thyroid gland after this time [673]. After injection of thyrotropic hormone, there is first an outflow of the iodine store present in the thyroid gland. This is rapidly followed by enlargement of the thyroid epithelium cells, and subsequently by third effect — a considerable rise in their capacity for uptake of iodine [674, 675, 676, 677] (cf. page 100). This increased tendency to iodine storage appears about 8 hours after the administration of thyrotropic hormone [678]. After removal of the pituitary, the normal capacity of the thyroid gland to take up iodine is significantly lowered. However, even in hypophysectomized animals the affinity of the thyroid epithelium for iodine can be increased by pre-treatment with thyrotropic hormone [679]. It has also been shown by the use of radioactive iodine that the formation of the thyroid hormone thyroxine from diiodotyrosine is promoted by thyrotropic hormone [673]. Apart from the quantity of radio-iodine stored in the thyroid gland, function can also be assessed by the measurement of the blood content of radioactive iodine and its excretion in the urine. By determination of the amount of iodine in each of 6-hourly portions of urine, characteristic excretion curves can

special literature and the brochure ACTH "Schering A.G. Berlin" must be consulted.

Thyrotropic Hormone

Whereas with thyroid hormone only a substitution therapy is possible, administration of thyrotropic hormone (Primothyron) restores thyroid function to normal in a physiological manner, and thus achieves a secretion of thyroid hormone adapted to the needs of the body. An effect of Primothyron on the thyroid gland can however only be expected if thyroid tissue capable of function is still present.

Animal experiments and clinical trials have shown that employment of thyrotropic hormone is indicated in the following conditions:

Use of Primothyron in diagnosis and treatment with radioactive iodine

Isotope research during recent years has contributed significantly to the knowledge of thyroid activity. In this technique, radioactive so-called "labelled" substances are used to follow their progress through the organism. In particular, iodine metabolism in the thyroid gland and the influence of the pituitary upon it have been studied in detail.

The iodine isotope I^{131} is now used as the radioactive substance. Distribution of the administered dose of radio-iodine in the organism, and its accumulation in the thyroid gland, are measured with a Geiger-Müller counter. The dose employed is usually 100 microcuries of radioactive iodine (1 microcurie is the disintegration of 3.7×10^4 atoms per second) dissolved in distilled water, sometimes with small amounts of potassium iodide as so-called "iodine carrier", this dose is given to the patient by mouth.

The thyroid gland is the organ richest in iodine. Its avidity for any iodine supplied, its capacity for using the iodine in hormone synthesis, and its ability also to store iodine in large amounts,

cause clinically they often produce only the symptoms of a hyperthyroidism, and their rapid metastasis to the lungs commonly remains undetected. In 1948 the important observation was made for the first time that by administration of thyrotropic hormone the iodine uptake of malignant thyroid tissue could be considerably increased [688]. In the same studies it had been found that thyroidectomy or the functional elimination of the gland by radio-iodine increases the iodine uptake of metastases of thyroid tumours. Since experience had shown that lowering the level of thyroid hormone in the blood induced an increase in output of thyrotropic hormone (cf. page 100), it was concluded that the above observation of increased iodine storage by metastases was due to the effect of thyrotropic hormone.

The practical significance of the above facts is that it is now possible by treatment with thyrotropic hormone to render thyroid tumours which were incapable of taking up iodine able to do so. As a result, it is possible to ensure retention of therapeutically effective amounts of radioactive iodine in the carcinomatous tissue [689]. The iodine affinity of many otherwise refractory metastases of thyroid carcinoma can also be increased by administration of thyrotropic hormone to such an extent that they can be successfully treated subsequently with radio-iodine [690].

Clinical experience in the employment of Primothyron in assessment of thyroid function with isotopes and in the treatment of malignant thyroid tumours with radio-iodine is still too limited for exact schedules of dosages in these conditions to be laid down.

Hypothyroidism and myxoedema

In conditions of thyroid hypofunction, the most marked of which appears as the clinical picture of myxoedema, the gland can be activated by treatment with thyrotropic hormone. In cases of myxoedema treated with Primothyron a significant rise in basal metabolism has been observed. The symptoms of myxoedema often disappear within a few days of the beginning of hormone

be plotted for the various forms of thyroid disturbance [668, 671, 672].

After administration of Primothyron, the responsiveness and functional state of the thyroid gland can be evaluated from the degree of iodine storage or its absence. Whereas comparison of basal metabolism assessed by the usual technique for evaluation of thyroid function with the clinical condition shows a discrepancy in 33% of cases, the results of the radio-iodine test correspond with the clinical condition in 94.3% of patients [666]. The employment of thyrotropic hormone in conjunction with radioactive iodine is today regarded as the most reliable method of assessment of thyroid function.

2. *Employment of Primothyron in the treatment of malignant thyroid tumours with radio-iodine*

Radioactive iodine is now employed not only for the treatment of thyrotoxicosis [680], but also specially in the therapy of malignant tumours of the thyroid gland and their metastases [681, 682]. For this purpose the auto-radiation of the iodine isotopes is utilized therapeutically, since it destroys tumour tissue without injuring the surroundings. An advantage over the customary methods of irradiation consists in the possibility of making the radioactive substance act directly in the tumour cells, because of the affinity of the thyroid tissue for iodine [683]. Radio-iodine has also proved useful in the discovery of metastases of thyroid gland carcinoma [681]. One disadvantage of radio-iodine therapy of thyroid carcinoma is that only about 50% of these tumours and their metastases are still capable of storing iodine to such an extent that the therapeutic radiation dose in the tissue can be attained [673, 685]. A proportion of thyroid tumours, particularly the differentiated adenocarcinomata of the gland and their metastases, no longer possess the property of taking up iodine [673, 686, 687]. The tendency of these tumours to very low iodine uptake is particularly unfortunate from the diagnostic standpoint, be-

A trial of thyrotropic hormone therapy is always indicated in Simmonds's cachexia. In many cases, Primothyron brings about a surprising and often sudden improvement in the whole clinical picture [695]. Thyroid gland preparations have little effect on the disturbances in panhypopituitarism and do not increase the depressed metabolic functions at all, since there is always a more or less marked thyroxine resistance in these patients. On the other hand, thyrotropic hormone first causes a rise in the specific dynamic action of protein on metabolism, and a rise in urate formation [696]. This is followed by a significant rise in basal metabolism. By the treatment with thyrotropic hormone the existing thyroxine resistance is also simultaneously overcome. With this therapy, the severe adynamia, asthenia and loss of appetite usually disappear with surprising rapidity [694]. The dosage recommended is 500 guinea-pig units i.m of Primothyron daily until improvement in the total picture appears.

Endocrine obesity

Apart from dystrophia adiposo-genitalis (Fröhlich type), which is characterized by the simultaneous appearance of obesity and hypogenitalism (cf. page 171), there is a generalized endocrine obesity of pituitary or thyrogenous origin. These two forms of obesity are favourably influenced by administration of thyrotropic hormone The rise in basal metabolism due to Primothyron leads to an increase in combustion of carbohydrate. This, together with the simultaneous disintegration of fat in the tissues, causes a considerable loss in weight. In these cases, activation of thyroid function by thyrotropic hormone also leads to regulation of mineral and water balance in the organism, and thus to loss of great quantities of fluid retained both intracellularly and extracellularly Hence, thyrotropic hormone can cause significant improvement in endogenous forms of obesity [697]. The dosage is 500 guinea-pig units of Primothyron i.m. 3 times a week for three weeks The course may be repeated after an interval of 1 to 2 months.

treatment. In this condition, the chief features which are changed by administration of thyrotropic hormone are the lowered basal metabolism, the loss of hair, the bradycardia, the lowered body temperature, the secondary anaemia and the severe constipation. Dryness of the skin and brittleness of the nails, which is often present, also regress rapidly [691, 692]. Simultaneously with the improvement in clinical symptoms and signs there is in most cases a disappearance of the characteristic apathy and a marked quickening of all mental functions [693]. A prerequisite for successful treatment of states of thyroid hypofunction, and particularly myxoedema, with thyrotropic hormone is of course the presence *of still responsive, i.e. potentially functional, thyroid gland* tissue. Experience has shown that a suitable dosage for the treatment of myxoedema is the daily injection intramuscularly of *500 guinea-pig units of Primothyron In milder cases of hypothyroidism,* 2 or 3 doses a week of 500 *guinea-pig units Primothyron* are sufficient. In these conditions, treatment with thyrotropic hormone should not be continued for more than 3 weeks. In many cases a permanent result is obtained only by repeating such courses of treatment several times with interpolation of rest periods of 4—6 weeks.

Simmonds's cachexia (panhypopituitarism)

The clinical picture of Simmonds's cachexia depends on a high-grade insufficiency or complete absence of all functions of the anterior pituitary In addition, an essential part is probably played by diencephalic disturbances, and especially lesions of the infundibulotuberous centres [691]. The difficulties of giving really significant treatment of this severe disease, which often leads irreversibly to death, and the need for adaptation of therapy to the individual case have already been discussed on page 202. The value of desoxycorticosterone treatment was mentioned on page 198, the employment of ACTH on page 201, and the suitability of treatment with gonadotropic hormones in association with sex hormones on page 202.

formation, under the influence of thyrotropic hormone [702]. The clinical observation that in human subjects administration of both thyrotropic hormone and of thyroxine favours wound healing and in some cases significantly accelerates it has also been confirmed by exact experiments in animals [703, 768]. The duration of healing of wounds inflicted on guinea-pigs experimentally under fully controlled conditions was lowered by 31% by Primothyron treatment in comparison with controls. For promotion of healing of fractures and large soft-part wounds intramuscular injection of 500 guinea-pig units of Primothyron 2—3 times a week has proved valuable.

Anaemia, secondary

Effects of thyrotropic hormone on blood formation have been observed both in man and in animal experiments. In the rabbit, repeated administration of thyrotropic hormone in doses of 50 guinea-pig units per kilo body weight has been found to raise the haemoglobin value as well as the erythrocyte, reticulocyte and thrombocyte counts. The white cell count shows a neutrophilia with a simultaneous relative lymphopenia. In the bone marrow, increased erythropoiesis and leucopoiesis were demonstrable [704].

In healthy men, both the red and the white cell pictures are completely unaffected even by repeated injections of thyrotropic hormone. On the other hand, its administration to patients with a secondary anaemia leads to stimulation of blood formation with increase in both erythropoiesis and leucopoiesis, provided that sufficient potentially functional bone marrow is still present The haemoglobin content of the erythrocytes is raised on an average by 5—9%. This therapeutic effect is particularly marked in secondary anaemias of elderly persons. For this condition, a suitable dosage is 500 guinea-pig units of Primothyron intramuscularly every other day After a course of six injections a significant stimulation of haematopoiesis is usually demonstrable.

Prevention of operative shock and postoperative thrombosis

Surgeons have reported observations according to which brief preoperative treatment with thyrotropic hormone may prevent to a large extent shock and collapse after operation, and the appearance of postoperative thrombosis and embolism [243, 698]. This is explicable through the total action of thyrotropic hormone. This leads via thyroid activation to increased oxidation, removal of residua, and hence finally to improvement in all autonomic functions in the organism. The actions of thyrotropic hormone which are of decisive importance in this respect are the increase in basal metabolism, the increase and acceleration of the circulating blood mass, and the increase in alkali reserve. By pre-treatment with Primothyron, the resistance of devitalized patients representing poor operation risks can be raised so far that even major interventions are well tolerated. Experience in hospitals has shown that in all poor-risk subjects an increase in basal metabolism of 20% before operation is worth attempting. The only contraindication to this pre-treatment is the existence of hyperthyroidism [699]. Before operation it is advisable to inject daily on each of 3 successive days 500 guinea-pig units of Primothyron i. m. The optimum effect usually appears after 3 injections, so that operation at this point can be undertaken with the least risk of the patient.

Fracture and wound healing

In animal experiments with artificially produced fractures, hyperaemia of the fracture site, which is the prerequisite for good callus formation, appears much earlier after administration of thyrotropic hormone than in controls and continues much longer [700]. Increase in hyperaemia at the fracture site has also been observed [701]. This effect is explained by the general increase in metabolism caused by thyrotropic hormone. Similar observations have been reported during clinical treatment of poorly healing fractures, especially in older patients with delayed callus

Do not discontinue therapy abruptly, but slowly taper it off.

Duogynon: *Substitution and stimulation therapy*

V. Every 3rd or 4th day 1 ampoule (20 mg. progesterone plus 2 mg. oestradiol benzoate) i. m., until about 4 weeks beyond the time of former abortions.

Abortion, threatened

Proluton: *Substitution therapy*

I. With the patient in bed, give 10 mg. i. m. once or twice a day until bleeding stops.
Subsequently, as in habitual abortion or

II. Begin treatment with 1 or 2 ampoules of 20 mg. Proluton intravenous or

Progynon M: *Stimulation therapy*

III. 5 times a day 1 tablet orally, or maybe more.
Further treatment as for habitual abortion.

Duogynon: *Substitution and stimulation therapy*

IV. One ampoule i. m. (20 mg. progesterone plus 2 mg. oestradiol benzoate) daily.
Further treatment as for habitual abortion.

Acne juvenilis sive vulgaris

In both sexes

Progynon ointment: *Substitution therapy if the male sex hormone predominates*

I. Twice daily 1—2 g. = 6—12 cm. length of ointment, to be applied to the affected parts of the skin, together with

Guide to Therapy and Suggestions for Dosage

Arranged alphabetically by indications

The following suggestions only represent g u i d e l i n e s for therapy. In actual practice, deviation from the dosage suggested will not infrequently be found necessary (cf. page 103). The reader will undoubtedly be surprised by the number of suggestions made in some cases. The necessary choice is however facilitated for him by the layout of the material. It is clear that the mechanism of action indicated with each suggestion for therapy only approximates to the physiological process, which is usually very complicated.

Abortion, habitual

Proluton: *Substitution therapy*

I Twice a week 5 mg i. m. for at least the first half of pregnancy *or*

II One or two 100 mg tablets by implantation
Duration of effect 8—12 weeks
If necessary, repeat *or*

Proluton C.

III One 5 mg dragee 3 times a day from the beginning of pregnancy until 4 weeks beyond the time at which abortion has taken place in the past
In addition, at around the time of expected periods, 5 mg Proluton i. m. on 3—5 successive days *or*

Progynon M: *Stimulation therapy*

IV. One tablet orally 3 times a day, from the 4th month 2 tablets 3 times a day without interruption.

a) Acute Addisonian crisis

Primocort intravenous:

50 mg. i. v., may be given several times a day; best combined with intravenous infusion of 1,000 c.c. physiological saline with 1 g. ascorbic acid, 10 g. dextrose, 5 g. sodium citrate and 10 g. sodium chloride. In addition, peripheral circulatory stimulants.

b) Maintenance treatment

Primocort:

I. 5—40 mg i. m daily, according to the degree of adrenal cortical damage. Attention to diet! (cf. page 186).

Primocort implants:

II. After establishment of individual hormone requirements, with *Primocort* i m., maintenance treatment may be continued by means of *Primocort implants.*

According to the patient's condition, 2—5 implants, each of 100 mg., are introduced at one session. Duration of effect 3—5 months

For recognition of overdosage, serial studies of weight, blood pressure, and salt and potassium values in serum are indispensable!

Addisonism (minor cortical deficiency)

Primocort tablets: *Substitution therapy*

I. One tablet buccally 3—4 times a day, according to the severity of the signs **or**

Primocort:

II. 5 mg. i m. daily or every other day.

Progynon C:

II. Two tablets daily orally or

Progynon B oleosum:

III 1 mg i m. 2—3 times a week or

Progynon drops:

IV. 10 drops perlingually 3 times a day.

Primocort:

V. In severe cases, at the beginning 5—10 mg. i. m. 2—3 times a week.

Primocort tablets:

VI. One tablet buccally 2—3 times a day for at least 3 weeks or

VII. Further treatment after initial intramuscular administration as in V.

In certain cases in the m a l e, also

Testoviron: *Substitution therapy if oestrogens predominate*

VIII Initially, 10 mg i. m daily, later 10—25 mg i m twice a week

During hormone therapy, the usual local treatment should not be neglected!

Acrocyanosis — see Circulatory disturbances

Acromegaly, especially if osteoporosis is present

In b o t h sexes:

Testoviron: *Anabolic and anti-pituitary effect*

I. 50 mg. i m daily for 2—3 months.

Progynon M:

II. One tablet orally 5 times a day.

With more marked uterine hypoplasia:

Progynon B oleosum forte: *Growth stimulation*

II. Five doses of 5 mg. i. m. at 4-day intervals; 3 to 6 rhythmical cycles with 8-day intervals between.

Progynon implants:

III. 20 mg, possibly repeated after 2—4 months

Best implanted in the neighbourhood of the uterus (labia majora)

After the uterus has grown sufficiently, treatment continues according to the Kaufmann schedule.

Priantin: *Stimulation therapy*

IV. 1,000 i u. intramuscularly 2—3 times a week in the 1st two weeks followed by

Primogonyl:

1,000 i. u intramuscularly on the 14th, 20th and 24th days. Repeated several times

In addition maybe vitamin E and short-wave therapy to the central nervous system.

Amenorrhoea, secondary — see also Sterility

Of less than 1 year's duration

Duogynon: *Symptomatic therapy*

I. One ampoule (20 mg. progesterone plus 2 mg. oestradiol benzoate) i. m on 2 successive days, repeated rhythmically on 2 occasions shortly before the next dates of periods.

If Duogynon therapy fails, or if amenorrhoea has lasted longer, Kaufmann schedule (see page 224)

or

Proluton:

II 5—10 mg i. m on 5 occasions, or more, between the 14th and 28th days

Adnexitis — see Salpingitis, chronic

Ageing, signs of — see Climacteric

Ageing, hard hearing due to *Promotion of circulation*

In women:

Progynon B oleosum:

1 mg. i. m. twice a week and

Testoviron tablets:

One 5 mg. tablet buccally twice a day.
Each course lasting for 3—5 weeks.

In men:

Testoviron:

10—25 mg. i. m. 3 times a week and

Progynon B oleosum:

1 mg. i. m. twice a week.
Each course lasting for 3—5 weeks.

Alopecia *Promotion of peripheral circulation*

Progynon B oleosum:

In addition to other measures, 1 mg. i. m. 2—3 times a week.

Amenorrhoea, primary

I. Kaufmann's schedule:

Progynon B oleosum forte: *Substitution therapy*

Five doses of 5 mg. i. m. at 4-day intervals, followed by

Proluton:

From the 21st day on, 5—10 mg. i. m. or even more, on 5 successive days.

Repetition of this artificial cycle three times.

Arthropathies, endocrine (in the climacteric) — see also Joint disorders *Substitution therapy*

In the female:

Progynon B oleosum:

1—5 mg. i. m. twice a week.
On improvement, do not discontinue suddenly, but prolong intervals between injections!

In the male:

Testoviron:

I. 25 mg. i. m 3—4 times a week; from the 2nd week on 10 mg i. m. 3—4 times a week; for about 4 weeks or

Testoviron-Depot.

II 50—100 mg i. m every 2—4 weeks or

Progynon B oleosum:

III As for women

Asthma, bronchial in women (premenstrual form)

Proluton: *Antioestrogenic therapy*

I. 5—10 mg. i m. 3 times in the last 2 weeks before the period begins or

Testoviron

II 10—25 mg i m 3 times a week, especially in the premenstruum

Asthma, bronchial

a) Tendency to asthma

ACTH "Schering A.G. Berlin": *Anti-allergic effect*

I. 30—40 i. u daily i. m. in equal 6-hourly doses for 2—4 days. Then gradual reduction in dose with increase in injection intervals to 8 hours. Total length of treatment 8—12 days.

Progynon drops:

III. 10 drops perlingually 3 times a day — *Substitution therapy* — or

Progynon dragees:

IV. One dragee buccally 3—4 times a day — or

Progynon C:

V 2 tablets a day orally for 20 days
Followed by *Proluton* as in II — or

Priantin and Primogonyl:

VI. As for primary amenorrhoea under IV — *Stimulation therapy*

Anaemia, secondary

Primothyron:

Every 2nd day 500 guinea-pig units i m
A total of 6—8 injections usually suffices

Angina pectoris

Promotion of circulation and cardiac output

In the male:

Testoviron-Depot:

I. Every 2—4 weeks 50—100 mg. i. m. — or

Testoviron:

II 10—25 mg daily i m for 1—3 weeks, later

Testoviron tablets:

One 5 mg tablet buccally 3 times a day

In the female:

Progynon B oleosum:

I 1 mg i m 4—6 times a week — or
II 5 mg i m once or twice a week

Anovulatory cycle — see Sterility

c) In milder cases:

Primocort tablets:

One tablet buccally 3—4 times a day.

d) In cholangitis with secondary damage to liver parenchyma:

Primocort implants:

According to the condition, 1—4 implants each of 100 mg. introduced at a single session subfascially.

Bleeding — see Hypermenorrhoea, Polymenorrhoea, Metropathia haemorrhagica cystica and Bleeding in adolescence.

Bleeding in adolescence *Substitution therapy*

Proluton:

I. Daily 5—10 mg. i. m. in the 2nd half of the menstrual cycle or during the bleeding for at least 5 successive days or

Testoluton forte:

II. One ampoule (25 mg. testosterone propionate plus 10 mg. progesterone) i. m. on each of 3 successive days during the bleeding.

If bleeding has persisted for a long time:

Progynon B oleosum:

III Daily 5 mg i m. on each of 5 successive days.

For prevention of recurrence:

Testoluton:

One ampoule (15 mg. testosterone propionate plus 10 mg. progesterone) i m. on each of 3 successive days before the period is expected to begin.

Primocort: *Restoration of iso-ionic condition in blood*

II. On the first day, 30 mg. i m; on the following days 10 to 20 mg i. m.; continue therapy to a total dose of about 200 mg. Recurrence of tendency to asthma after treatment to be countered at once by immediate injection of 20 mg. *Primocort* i. m On the following days, further injections of 10 mg daily up to a total dose of 80—100 mg

b) Status asthmaticus:

ACTH "Schering A.G. Berlin": *Anti-allergic effect*

I. 70—80 i. u. daily i. m. in equal 4-hourly doses until the status is arrested.

Primocort: *Restoration of iso-ionic condition in blood*

II Immediately after relief of bronchospasm by a spasmolytic, 50 mg Primocort i v. followed by 20 mg Primocort i m

c) Severe chronic cases:

ACTH "Schering A.G. Berlin": *Anti-allergic effect*

40—60 i. u. daily i. m. in equal 6-hourly doses for 5—7 days. Then gradual reduction in dose. Duration of treatment 2—4 weeks.

Azoospermia — see Sterility

Biliary disorders *Liver protection; spasmolytic and analgesic effect*

a) Acute conditions·

Primocort:

Daily 5—10 mg. i. m. to a total of 100—150 mg.

b) Chronic conditions:

Primocort:

Twice a week, 10 mg. i. m. to a total of 10—12 injections.

Breast, hypoplasia of *Local effect*

Progynon ointment:

Twice daily 1—2 g., i. e. 6—12 cm. of ointment locally.

In association with generalized hypoplasia — see Primary amenorrhoea.

Burns

ACTH "Schering A.G. Berlin": *Stimulation therapy*

I. High dosage to combat shock after burns!
Initially: 70—100 i. u. daily i. m, divided into 4 equal doses at 6-hourly intervals.
Further treatment: 20—50 i. u. daily i. m, divided into 3 equal doses at 8-hour intervals.
Towards the end of treatment: gradually tapering off!

Primocort i.v.: *Substitution therapy and protein detoxication*

II. 10, 25 or 50 mg. daily intravenously, according to the severity of the condition; possibly repeated. Further treatment with

Primocort:

10—20 mg. i. m daily.

Callus formation, promotion of — see Fracture healing

Carcinoma — see under the affected organ

Cardiac insufficiency — cf Angina pectoris

Testoviron: *Promotion of circulation and cardiac output*

10—25 mg. i. m. twice a week

Palliative treatment. The hormone therapy must be continued for as long as possible.

Testoviron-Depot:

I. 250 mg. i m., at first every 2 weeks, later every 3—4 weeks or

Testoviron:

II 50 mg i m 3—6 times a week, to a total of at least 3,000 mg

As auxiliary or after-treatment:

Testoviron implants:

III 200—400 mg subfascially every 6 weeks or

Methylandrostenediol:

IV 150—300 mg i m weekly, in 1—3 injections

Prophylactic treatment after operation and postoperative irradiation

Testoviron-Depot:

I Every 4 weeks 100 mg i m or

Testoviron implants:

II Every 6—8 weeks 200 mg subfascially

In women beyond the menopause, at least 5 years after the last period, preferably in cases with soft-part metastases:

Progynon M:

Three to five tablets daily, each of 0.2 mg., orally

Breast, chronic cystic disease of — see also Mastodynia

Testoviron:

I. Twice a week 10—25 mg. i. m., beginning a few days after the end of menstruation, continuing for several months.

Testoviron:

II. Every 2—3 days, 10—25 mg. into the breast, for 1—5 doses

Breast, hypoplasia of *Local effect*

Progynon ointment:

Twice daily 1—2 g., i. e. 6—12 cm. of ointment locally.

In association with generalized hypoplasia — see Primary amenorrhoea.

Burns

ACTH "Schering A. G. Berlin": *Stimulation therapy*

I. High dosage to combat shock after burns!
Initially: 70—100 i. u daily i. m., divided into 4 equal doses at 6-hourly intervals.
Further treatment· 20—50 i. u. daily i. m., divided into 3 equal doses at 8-hour intervals.
Towards the end of treatment gradually tapering off!

Primocort i. v.: *Substitution therapy and protein detoxication*

II 10, 25 or 50 mg. daily intravenously, according to the severity of the condition, possibly repeated. Further treatment with

Primocort:

10—20 mg. i m daily.

Callus formation, promotion of — see Fracture healing

Carcinoma — see under the affected organ

Cardiac insufficiency — cf Angina pectoris

Testoviron: *Promotion of circulation and cardiac output*

10—25 mg i m twice a week.

Castration, endocrine in women — cf. Carcinoma

Testoviron: *Anti-pituitary therapy*

50 mg. i. m. 8—10 times each cycle.

Castration, sequelae of

In w o m e n — see Climacteric and Amenorrhoea (Kaufmann's schedule on page 224).

In m e n — see Hypogenitalism.

Cholangitis — see Biliary disorders

Cholecystitis — see Biliary disorders

Cholelithiasis — see Biliary disorders

Circulatory disturbances *Peripheral effect*

Ulcer of leg, dead fingers, acrocyanosis, endangiitis obliterans, intermittent claudication, frostbite, vasoneurotic oedema, early Raynaud's syndrome, chilblains.

In w o m e n :

Progynon B oleosum:

I. 1 mg. i. m. daily for 4—5 days, with intervals between courses of 10 days. Treatment for several weeks.

In menstruating women, treatment only in the first half of the intermenstruum or

Progynon ointment:

II. Twice daily 1—2 g., i. e. 6—12 cm of ointment, locally.

In men:

Progynon B oleosum and *Progynon ointment:*

As in women; in addition

Testoviron:

10—25 mg. daily i. m.

Claudication, intermittent — see Circulatory disturbances

Climacteric — cf. Hypertension in the climacteric

Progynon C: *Anti-pituitary therapy*

I. One tablet orally daily or every other day. If needed, temporarily 2—3 tablets daily. Individual dosage! *or*

Progynon drops:

II. 10 drops perlingually 3 times a day *or*

Progynon dragees:

III. One 0.1 mg dragee buccally 2—3 times a day *or*
One dragee forte (1 mg) buccally *or*

Progynon B oleosum:

IV. 1 mg or even 5 mg i. m. once or twice a week *or*

Progynon implants:

V. Implants of 10 mg, after hysterectomy 20 mg
If needed, repeat after 2—4 months.

Primodian tablets:

VI. Initially 2 tablets 2—3 times a day orally (1 tablet contains 4 mg methyl testosterone plus 0.002 mg ethinyl oestradiol)

Maintenance dose 2—3 tablets daily

In cases of intolerance to Progynon, especially as a result of hyperoestrinism, in psychoses and depression:

Testoviron:

VII. 10 or even 25 mg., i. m. once or twice a week **or**

Testoviron-Depot:

VIII. 50—100 mg. i. m.

Repeated if necessary after 2—4 weeks **or**

Testoviron tablets.

IX One 5 mg tablet buccally 2—3 times a day

Climacteric, male *Substitution therapy*

Testoviron tablets:

I. One 5 mg. tablet buccally 1—3 times a day for 4—6 weeks **or**

Testoviron T:

II 10—15 drops transcutaneously 3 times a day for 4—6 weeks

In severe exhaustion states

Testoviron-Depot:

III. 50—100 mg i. m every 2—4 weeks **or**

Testoviron.

IV At first 10 mg daily i m for 4 days, then 2—3 times a week

Coma, diabetic (hyperglycaemic) *Promotion of carbohydrate utilization*

Primocort i.v.:

50 mg intravenously, repeated if need be, in combination with insulin therapy.

Coma, hepatic *Metabolic effect*

Primocort i.v.:

50—100 mg. intravenously, together with large doses of glucose by injection or intravenous drip infusion

Convalescence — see also Infectious diseases

Primocort tablets: *Metabolic effect*

One tablet buccally 2—3 times a day for at least 14 days.

Cryptorchidism *Stimulation therapy*

Primogonyl:

I. 150—1,000 i. u. once or twice a week i. m., according to age, so far as possible between the ages of 10 and 14. Total dose at least 5,000 i. u Also simultaneously

Testoviron:

II. 10 mg. i. m. once or twice a week.
Total dose up to 100 mg. or

Testoviron T:

III 5—10 drops transcutaneously twice a day.

Cushing's syndrome

Progynon B oleosum forte: *Anti-pituitary therapy*

5 mg. i. m. 3 times a week for several months.

After operative removal of an adrenal cortical tumour.

Primocort: *Substitution therapy*

5 mg i m 2—3 times a week for several months

Cystic glandular hyperplasia (metropathia haemorrhagica cystica)

Proluton: *Substitution therapy*

I 5—20 mg. daily i m., or even more, for at least 6 days until bleeding ceases or

Proluton i.v.:

II 20—40 mg. intravenously to begin treatment or

Testoviron:

VII. 10 or even 25 mg., i. m. once or twice a week or

Testoviron-Depot:

VIII. 50—100 mg. i. m.

Repeated if necessary after 2—4 weeks or

Testoviron tablets:

IX. One 5 mg tablet buccally 2—3 times a day.

Climacteric, male *Substitution therapy*

Testoviron tablets:

I. One 5 mg. tablet buccally 1—3 times a day for 4—6 weeks or

Testoviron T:

II 10—15 drops transcutaneously 3 times a day for 1—6 weeks

In severe exhaustion states:

Testoviron-Depot:

III. 50—100 mg. i. m. every 2—4 weeks or

Testoviron:

IV At first 10 mg daily i m for 4 days, then 2—3 times a week

Coma, diabetic (hyperglycaemic) *Promotion of carbohydrate utilization*

Primocort i.v.:

50 mg. intravenously, repeated if need be, in combination with insulin therapy.

Coma, hepatic *Metabolic effect*

Primocort i.v.:

50—100 mg intravenously, together with large doses of glucose by injection or intravenous drip infusion.

Primocort i. v.:

II Daily or every other day 5 mg together with 0.5 g vitamin C intravenously

Diabetes mellitus, particularly in the elderly

In women: *Anti-pituitary therapy; improvement of sugar metabolism*

Progynon B oleosum:

1—5 mg. i. m. twice a week.

In men:

Testoviron:

10—25 mg. i. m. daily; later

Testoviron-Depot:

100—250 mg. i. m. every 2—4 weeks;
later 50 mg. at the same intervals.

For follow-up treatment:

Testoviron tablets:

5 mg. buccally 3 times a day.

Diabetes in pregnancy

Progynon M:

Begin with 1 tablet orally daily (0.2 mg.) and increase to 9 tablets (minimum dose) daily at the end of pregnancy.

Diabetic retinitis

Testoviron:

10—50 mg i. m 2—3 times a week.

Diphtheria — see Infectious diseases

Testoluton forte: *Anti-oestrogen therapy*

III. One ampoule (25 mg. testosterone propionate plus 10 mg. progesterone) i. m. on each of 3 successive days or

Primogonyl:

IV. 1,000 i. u. every other day i. m.

To prevent recurrence:

Testoluton:

I. One ampoule (15 mg. testosterone propionate plus 10 mg. progesterone) i. m. at 3-day intervals during the last 10 days before the period begins or

Progynon B oleosum forte:

II. 5 mg. i. m. for 5 doses within the first 2 weeks after bleeding ceases, and then

Proluton:

10 mg. i. m. 3—6 times within the next 10 days

After more prolonged bleeding (stage of desquamation):

Progynon B oleosum forte: *Anti-pituitary therapy*

10—20 mg. i. m. within 3—4 days.
Followed by Kaufmann's schedule
(cf. Amenorrhoea).

Depression, endocrine

Sex hormones:

In w o m e n — see Climacteric, or Premenstrual symptoms or Psychoses

In m e n — see Climacteric, male or Psychoses.

In b o t h sexes:

Primocort: *Metabolic effect*

I. 5 mg. i. m. daily or every other day, immediately followed by 0.5 g. vitamin C i. v. or

Testoviron tablets: *Anti pituitary therapy*

IV. Two 5 mg tablets buccally 3 times a day for 8 days before the date of ovulation and up to its appearance

Proluton i.v.:

20 mg. intravenously to cut short the attack of pain.

For treatment when combined with other symptoms of hyperoestrinism, see under Hyperoestrinism

Dystocia (uterine inertia)

With postmature or dead foetus:

Progynon B oleosum forte:

5 mg. i. m twice a day for 3 days, possibly in combination with oxytocics.

Dystonia, vegetative — see Vegetative dystonia

Dystrophia adiposo-genitalis *Stimulation therapy*

In boys and men.

Testoviron:

I. According to age, 10 mg i m once or twice a week for 6 months or more or

Testoviron T:

II 5—10 drops transcutaneously twice a day or

Primogonyl:

III 300—1,000 i u once or twice a week i m, possibly in combination with *Testoviron.*

Dystrophy due to protein deficiency *Anabolic effect*

Testoviron-Depot:

I Every 2—3 weeks 50—100 mg i. m. or

Dwarfism, pituitary *Substitution therapy*

Primogonyl:

I. 300—1,000 i. u. twice a week i. m., according to age, for several months.

Priantin:

II. 5,000 i. u. 2—3 times a week i. m.; may be combined with Testoviron (see Growth, retardation of, *in* children)

Dysmenorrhoea *Substitution or stimulation therapy*

a) With uterine hypoplasia·

Progynon B oleosum:

I. One mg. i. m. 3—5 times during the first 14 days after menstruation.
Repeated several times or

Progynon dragees:

II Daily 2—3 dragees forte buccally or

Progynon drops:

III 10 drops 3 times a day perlingually, also timed in relation to the cycle

b) With a normally developed uterus: *Sedation*

Testoluton:

I. One ampoule (15 mg. testosterone propionate plus 10 mg. progesterone) i. m. daily on 3 days before menstruation, or shortly before pain is expected

Proluton:

II 5 mg. i. m. daily on each of 5 successive days before menstruation
Repeated several times or

Proluton C:

III Two 5 mg dragees 2—4 times a day for 8 days up to the beginning of the period
Repeated several times

In girls:

Progynon B oleosum:

One mg. i. m. weekly for not longer than 3 weeks.

In both sexes

Primogonyl

300 i. u for 4—6 doses i m at 3—4 day intervals

Epilepsy, in women *Substitution therapy*

a) With ovarian hypofunction:

Progynon B oleosum:

One mg. i. m. 5 times during the first 2 weeks of the menstrual cycle.

b) The premenstrual form:

Proluton:

5 mg i. m. on 5 successive days before the period begins.

Epiphysiolysis *Anabolic effect*

In both sexes:

Testoviron:

10—25 mg. i m. daily for several weeks.

Eunuchoidism — see Hypogenitalism

Exhaustion states — see also Climacteric and Dystrophy due to protein deficiency

a) Acute.

Primocort:

5—10 mg i. m. 2 or 3 times a week for 2 weeks, then 5 mg. i m. twice a week for 3 or 4 weeks.

Methylandrostenediol:

II 20—100 mg i. m 3 times a week,
Children: 10—20 mg. i. m. 3 times a week, according to age

or

Methylandrostenediol tablets:

III. One tablet buccally 2—3 times a day.

Ejaculatio praecox — see also Impotence

Testoviron: *Substitution therapy*

5 mg. i. m. 3 times a week, possibly combined with

Progynon B oleosum:

One mg. i. m. once a week.

Endometriosis *Anti-oestrogen therapy*

Testoviron:

I. 25 mg. i. m. daily or every other day.
Begin treatment about 1—2 weeks before a period

or

Testoviron-Depot:

II Every 3—4 weeks 100—250 mg i m

Endometritis, post partum and post abortum

Progynon B oleosum forte: Promotion of wound healing

5 mg. i m. daily for 3—5 days.
If bleeding does not cease, a placental polyp should be suspected!

Enuresis nocturna *Stimulation therapy*

In boys:

Testoviron T:

I. Twice a day 5—10 drops transcutaneously or

Testoviron:

II 10 mg. i. m once or twice a week.

Foetal death *Pituitary effect*

To induce labour:

Progynon B oleosum forte:

5 mg. i. m. daily for at least 4 days.

Follicle, persistence of — see Cystic glandular hyperplasia

Fracture healing, acceleration of *Metabolic effect*

Primothyron:

I. 500 guinea-pig units i. m. 2—3 times a week or

Testoviron:

II. 25 mg. i. m. 2—3 times a week

Frigidity

a) With ovarian hypofunction:

Progynon dragees: *Substitution therapy*

I. One dragee forte buccally 3 times a day or

Progynon B oleosum:

II. Five doses of 1 mg. i. m. within the first 20 days of the cycle

b) With normal genital function.

Testoviron tablets: *Stimulation therapy*

I. One 5 mg. tablet buccally twice a day or

Testoviron:

II. 25 mg. i. m. twice a week, possibly only in the secretory phase.

Frostbite — see also Circulatory disturbances

Primocort:

10—20 mg. i. m. daily.

Progynon ointment: *Peripheral effect*

1—2 g., i. e. 6—12 cm. of ointment twice a day.

b) Chronic:

Primocort tablets:

One tablet buccally 1—3 times a day for 6 weeks.

Eye diseases, inflammatory and allergic

ACTH "Schering A.G. Berlin": *Anti-inflammatory and anti-allergic action*

a) Acute conditions:

30—50 i. u. daily i. m. in equal 6-hourly doses for 3 to 4 days. Then gradual fall in dosage. Total duration of treatment 6—10 days.

b) Very severe or chronic conditions:

60 i. u. daily i. m., or more, in equal 4-hourly doses for 3—4 days. Then gradual fall in dosage, with daily maintenance dosage between 10 and 20 i. u. *intramuscularly in equal 8-hourly doses, for 10 to 14 days. Gradual tapering off. Duration of treatment 3—5 weeks.*

Fibroids, uterine *Anti-oestrogen therapy*

Testoviron-Depot:

I. 100—250 mg. i. m. every 3—4 weeks or

Testoviron:

II. 25 mg. i. m. daily or every other day for 14 days before and during menstruation

With menorrhagia:

Testoluton forte:

One ampoule (25 mg. testosterone propionate plus 10 mg. progesterone) i. m. on each of 3 successive days.

Fitness, increase in physical and mental — see Climacteric

Hair, falling — see Alopecia

Hearing, disturbances of — see Ageing, hard hearing due to

Hepatitis — see Liver diseases

Hirsutism *Anti-androgen effect*

Progynon B oleosum forte:

5 mg. i. m. 2—3 times a week, with the exception of the last week of the cycle, over prolonged periods.

Hyperemesis gravidarum — see Vomiting of pregnancy

Hypermenorrhoea, functional *Anti-oestrogen therapy*

a) For prophylaxis:

Testoluton:

One ampoule (15 mg testosterone propionate plus 10 mg. progesterone) i. m. on each of 3 successive days, shortly before the expected time of beginning of the period.

b) During bleeding·

Testoluton forte:

One ampoule (25 mg. testosterone propionate plus 10 mg. progesterone) i. m. on each of 3 successive days

Hyperoestrinism (hyperfolliculinism) — see under relevant symptoms·

Amenorrhoea, dysmenorrhoea, hypermenorrhoea, mastodynia, metropathia, migraine, polymenorrhoea, premenstrual symptoms.

Genital carcinoma — see Breast, carcinoma of

Gigantism — see Acromegaly

Glaucoma

Proluton:

10 mg. i. m. every other day.

In acute attacks:

Proluton i. v.:

20 mg. intravenously, and then *Proluton* i. m. as above.

Graves's disease in women (pituitary form)

Progynon B oleosum forte: *Anti-pituitary therapy*

5 mg. i. m. 3 times a week.

Growth, retardation of, in children — see also Dwarfism

In boys:

Testoviron:

5—10 mg. i. m. 3 times a week, according to age.

In both sexes:

Methylandrostenediol.

I. 10—20 mg. i. m. 3 times a week, according to age or

Methylandrostenediol tablets:

II. One 25 mg. tablet buccally 1—3 times a day, according to age

Haemophilia *Anti-androgen effect*

Progynon B oleosum:

1 mg. i. m. daily or every 2nd or 3rd day.

Raising of capillary tonus

Hypotension

Primocort:

I 5—10 mg. i. m. twice a week for 3—4 weeks or

Primocort tablets:

II. One tablet buccally 2—3 times a day for 6—8 weeks.

Stimulation therapy

Hypothyroidism

Primothyron:

500 guinea-pig units i. m. 2—3 times a week; not longer than 3 weeks If needed, repeat the course several times, with interpolation of 4—6 week rests.

Substitution therapy

Impotence — see also Ejaculation praecox

Testoviron:

I. 10 mg. i. m. 3—5 times a week.

After a result appears:

Testoviron tablets or

II One 5 mg tablet buccally 2—4 times a day or

Testoviron-Depot:

III Every 4—5 weeks, up to 250 mg i m or

Testoviron T:

IV 10—15 drops transcutaneously 3 times a day

Stimulation therapy

Primogonyl:

V. 300—1,000 i. u. 1—3 times a week i. m.

Peripheral effect

Incontinence of urine

Progynon C: or

I. 1—2 tablets orally daily

Progynon implants:

II 10 mg at intervals of 2—3 months

Hypertension in the climacteric

Testoviron-Depot:

100 mg. i. m. every 2—3 weeks.

Hyperthyroidism — see Graves's disease

Hypogenitalism *Substitution thera[py]*

In w o m e n — see Amenorrhoea

In m e n :

a) Primary testicular insufficiency:

Testoviron-Depot:

I 250 mg. i. m. every 3—6 weeks or

Testoviron:

II. 10—25 mg. i. m. 3—5 times a week.

For long-term treatment:

Testoviron tablets:

I. 5 mg buccally 2—4 times a day *or*

Testoviron implants:

II. 100—200 mg at intervals of 2—3 months

b) Secondary hypogonadotropic form:

Primogonyl: *Stimulation therapy*

1,000 i. u. 3 times a week i. m.

In b o y s — see Cryptorchidism

Hypomenorrhoea — see Oligomenorrhoea

Often no treatment is needed.

Hypoplasia of uterus — see Amenorrhoea

Raising of capillary tonus

Hypotension

Primocort:

I. 5—10 mg i. m. twice a week for 3—4 weeks or

Primocort tablets:

II. One tablet buccally 2—3 times a day for 6—8 weeks.

Stimulation therapy

Hypothyroidism

Primothyron:

500 guinea-pig units i. m 2—3 times a week; not longer than 3 weeks. If needed, repeat the course several times, with interpolation of 4—6 week rests.

Substitution therapy

Impotence — see also Ejaculation praecox

Testoviron:

I. 10 mg i. m. 3—5 times a week

After a result appears:

Testoviron tablets:

II One 5 mg tablet buccally 2—4 times a day or

Testoviron-Depot:

III Every 4—5 weeks, up to 250 mg i m or

Testoviron T:

IV 10—15 drops transcutaneously 3 times a day or

Stimulation therapy

Primogonyl:

V 300—1,000 i u. 1—3 times a week i. m.

Peripheral effect

Incontinence of urine

Progynon C:

I. 1—2 tablets orally daily or

Progynon implants:

II 10 mg at intervals of 2—3 months

Induratio penis plastica (Peyronie's disease) *Peripheral effect*

Progynon B oleosum forte:

5 mg. i. m. every 2nd—3rd day.

After a result appears (3 to 4 weeks), lower the dose.

Infantilism: in women — see Amenorrhoea
in men — see Hypogenitalism

Infectious diseases

Primocort:

I. In severe cases, 5—20 mg. i. m. daily.
In milder cases, 5—10 mg. i. m. 2—3 times a week.

Primocort tablets:

II. After improvement sets in, and for after-treatment, one tablet buccally 2—3 times a day.

In chronic infections with protein depletion

Testoviron-Depot: *Anabolic effect*

III. 100—250 mg. i. m. every 4—5 weeks, repeatedly.

Methylandrostenediol:

IV 20—100 mg i. m. 3 times a week
In children, according to age, 10—20 mg i. m. 3 times a week for several weeks.

Insulin shock treatment, improvement in

Primocort: *Promotion of carbohydrate utilization*

10 mg. i. m. on the evening before each insulin shock.

Jaundice — see Liver diseases

Joint diseases chronic degenerative, deforming — see also Arthropathies

Primocort (combined with ***Vitamin C***): *Local effect*

I. 5 mg. ***Primocort*** i. m. followed within at most 5 minutes by 1 g. ***Vitamin C*** intravenously **or**

II. 5 mg. ***Primocort*** intravenously plus 1 g. ***Vitamin C*** in the same syringe **or**

III. 5 mg. ***Primocort*** plus 1 g ***Vitamin C*** in the same syringe intramuscularly.

The technique of these injections must be strictly adhered to, since the therapeutic results depend absolutely on this Repeat combined injections according to duration of freedom from pain and improvement in joint function. If there is no response after two repetitions, *further treatment is useless.*

Primocort implants:

IV After 4 days of treatment with combined injections, therapy may be continued by subfascial introduction of a 100 mg implant In this case, no further supplementary vitamin C is needed

Labour, induction of — see Dystocia and Foetal death

Lactation, suppression of *Anti-pituitary therapy*

Progynon B oleosum forte:

I. 5 mg. i. m. twice a day for 2—4 days **or**

Progynon C:

II On the 1st and the 2nd day, 9 tablets daily,
on the 3rd and 4th days, 8 tablets daily,
on the 5th and 6th days, 7 tablets daily,
in divided doses orally **or**

Testoviron:

III 50 mg i m daily for 6 days

Leucorrhoea, cervical (hypersecretion) *Anti-oestrogen therapy*

Testoviron:

25 mg. i. m. 2—3 times a week from the 9th day of the cycle.

Leucorrhoea, vaginal (with ovarian hypofunction)

Progynon drops: *Substitution therapy*

I. 10 drops 3 times a day perlingually or

Progynon B oleosum:

II. 1 mg i m 2—3 times a week. One week's rest before the period or

Progynon ointment:

III For tampon treatment

Liver atrophy, acute yellow *Metabolic effect*

Primocort i. v.:

50—100 mg intravenously daily by injection or drip infusion in association with large doses of glucose.

Liver diseases *Metabolic effect*

a) In acute conditions.

Primocort:

I. Daily or several times a week 10 mg. i m or

Primocort i. v.:

II. *Daily 10 mg. intravenously, possibly several times* or

III. 25—50 mg. as addition to intravenous infusions of 300—500 c.c. 5% glucose solution.

b) In chronic damage to the liver parenchyma:

Primocort:

I. 10 mg. i. m. twice a week or

Primocort tablets:

II. One tablet buccally 3—4 times a day or

Primocort implants:

III. One to 3 implants, each of 100 mg., introduced simultaneously subfascially.

In addition to *Primocort* treatment, administration of vitamin B and vitamin C is advisable

Liver, cirrhosis of

In the male.

Testoviron:

25 mg. i. m. twice a week.

Liver protection — see also Liver diseases and Biliary disorders

Primocort: *Metabolic effect*

In diseases in which liver function is endangered, prophylactically 5 mg i. m. 2—3 times a week, followed by

Primocort tablets:

One tablet buccally 2—3 times a day for several weeks.

Lupus erythematosus, especially the acute disseminated form

ACTH "Schering A. G. Berlin"

Initially, 70—80 i. u. daily i. m. in equal 4-hourly doses for 14—20 days.

If there is no response to these initial doses, even higher daily doses up to 120 units i. m. for several days. Then gradual lowering of dosage as in rheumatoid arthritis. Maintenance therapy may be given with daily doses between 15 and 40 i. u. i. m. for several weeks.

Mastodynia in the premenstruum (hyperfolliculinism or hyperoestrinism) *Anti-oestrogen therapy*

Testoluton:

I. Every 3 days, one ampoule (15 mg. testosterone propionate plus 10 mg. progesterone) i. m., beginning 10 days before the menstrual period, or

Testoviron T:

II. 20 drops locally twice a day or

Testoviron tablets:

III One 5 mg. tablet buccally twice a day during the same period of time

Mastopathy, chronic cystic — see Breast, chronic cystic disease of

Menstruation, retardation of — see Polymenorrhoea

Metropathia haemorrhagica cystica — see Cystic glandular hyperplasia

Migraine

a) With ovarian hypofunction.

Progynon B oleosum: *Substitution therapy*

One or 5 mg. i. m. twice a week for 20 days.

b) Premenstrual form (hyperoestrinism or hyperfolliculinism)

Testoluton: *Anti-oestrogen therapy*

One ampoule (15 mg. testosterone propionate plus 10 mg. progesterone) i. m. at 3-day intervals during the last 10 days before the period begins.

Myasthenia gravis *Stimulation therapy*

Primocort:

I. 5—10 mg. daily i. m. for several weeks, with additional vitamin B and vitamin C or

Testoviron:

II. 25 mg. i. m twice a week.

Myocardial infarction — see also Angina pectoris

Improvement of myocardial metabolism, effect on blood pressure

Primocort i.v.:

Immediately, 50 mg. intravenously, possibly several times in the day, to avoid the fall in blood pressure which threatens life.

Then, 50 mg. intravenously once or twice a day for 3 days, and simultaneously 10—20 mg. *Primocort* daily i m Further treatment with

Primocort:

10—20 mg. i. m. daily for the next 5 days, then 5—10 mg i. m daily or every other day for a further 3—4 weeks.

Myoma of uterus — see Fibroids

Myxoedema *Stimulation therapy*

Primothyron:

500 guinea-pig units daily i. m. for 3 weeks.
Several series may be given, with interpolation of 4—6 week rests

Necrospermia — see Sterility

Nephropathies *Anabolic or renotropic effect*

a) In acute degenerations (cholera, mercury poisoning, and similar diseases):

Testoviron:

50 mg. i. m. daily.

b) In chronic degenerations:

Testoviron:

25 mg. i. m. 3 times a week.

Nephrotic syndrome

ACTH "Schering A. G. Berlin":

Daily 80—100 i. u. in equal 4-hourly doses i. m. for 12 successive days at the most.

When diuresis sets in, reduce the initial dose by one-third. Further treatment with the reduced dose for 3 days, then reduction of the dose by a further third, and finally closure of treatment with daily doses of 7.5 to 5 i. u. i. m. for 3 days.

If after 12 days on the maximum dosage no diuresis of note has set in, an attempt may be made to produce a sudden flow of urine by suddenly interrupting the ACTH treatment. Abrupt interruption is however permissible only in exceptional cases!

If the urine excretion remains unsatisfactory, repeat the course after a 5—8 day interval.

Keep to the usual diet for nephrosis during the ACTH course.

Nipples, cracked *Local effect*

Progynon ointment:

Apply 1—2 g. (= 6—12 cm of the ointment) to the affected parts twice daily

Obesity of endocrine origin

In b o y s and m e n: see Dystrophia adiposo-genitalis.

In w o m e n with ovarian hypofunction:

Progynon B oleosum: *Substitution therapy*

1 mg. i m on 5 occasions within 20 days, correctly timed in relation to the cycle, followed by

Proluton:

5 mg i m on 5 successive days

In b o t h sexes with the thyrogenous form·

Primothyron: *Stimulation therapy*

500 guinea-pig units i. m. 3 times a week for 3 weeks Repeat after 1—2 months.

Oligomenorrhoea *Stimulation therapy*

Progynon B oleosum:

I. 1 mg. i. m. 5 times within 20 days after menstruation. Then

Proluton:

5—10 mg i. m. 2—5 times in the last 10 days before the next period or

Proluton·

II. Given alone, as in I

Progynon B oleosum forte:

III. 5 mg. i. m once on the 21st day of the cycle. Then

Proluton:

10 mg. i m. once on the 23rd day of the cycle, *or*

Progynon C:

IV Two tablets a day orally for 10 days after *menstruation*

Oligospermia — see Sterility

Nephropathies *Anabolic or renotropic effect*

a) In acute degenerations (cholera, mercury poisoning, and similar diseases):

Testoviron:

50 mg. i. m. daily.

b) In chronic degenerations:

Testoviron:

25 mg. i. m. 3 times a week.

Nephrotic syndrome

ACTH "Schering A. G. Berlin":

Daily 80—100 i. u. in equal 4-hourly doses i. m. for 12 successive days at the most.

When diuresis sets in, reduce the initial dose by one-third. Further treatment with the reduced dose for 3 days, then reduction of the dose by a further third, and finally closure of treatment with daily doses of 7.5 to 5 i. u. i. m for 3 days.

If after 12 days on the maximum dosage no diuresis of note has set in, an attempt may be made to produce a sudden flow of urine by suddenly interrupting the *ACTH* treatment. Abrupt interruption is however permissible only in exceptional cases[1]

If the urine excretion remains unsatisfactory, repeat the course after a 5—8 day interval.

Keep to the usual diet for nephrosis during the *ACTH* course.

Nipples, cracked *Local effect*

Progynon ointment:

Apply 1- 2 g. (= 6- 12 cm. of the ointment) to the affected parts twice daily

b) Treatment:

Primocort i.v.:

I. 50 mg. intravenously, possibly several times a day

or

II. 25—50 mg. added to an intravenous infusion of salt or glucose, after the acute circulatory crisis has been overcome by analeptics subcutaneously or i. m.

c) To combat the postoperative loss of chloride:

Primocort i.v.:

I 5—10 mg. intravenously or

II. 25—50 mg. in an intravenous infusion of salt or glucose.

Continuation of Primocort medication:

In a)—c) always several days after operation.

d) Prevention of operative shock.

Primothyron: *Increase in tissue oxidation*

500 guinea-pig units i. m. daily for 3 days before the operation. The optimum effect is generally obtained after the third injection. At this point, the operation carries the least risk to the patient.

Orchitis

In mumps, as prophylaxis or with beginning orchitis:

Progynon B oleosum forte:

One dose of 5 mg i. m.

Osteoarthritis — see Joint diseases

Operation, preparation for *Metabolic and circulatory effects*

Primocort:

I. 10 mg. i. m. daily for several days before the intervention or

Primocort i.v.:

II. 5—10 mg. intravenously daily or

III. 25—50 mg. daily added to an intravenous infusion of glucose.

Testoviron:

IV. On each of the 2 days before the operation, 50 to 100 mg. i. m.; after the operation, 50—25 mg i. m. daily in descending dosage.

Operations, abdominal in pregnancy

Proluton: *Substitution therapy*

10 mg. i m. daily on the day before and several days after the operation.

After vaginal operations, especially plastic ones:

Progynon B oleosum: *Peripheral effect*

I. 1 mg. i m. daily for 14 days.

Progynon ointment:

II. Apply locally every day.

Operative shock

a) Prophylaxis:

Primocort: *Metabolic and circulatory effects*

I. 10—20 mg. i. m. immediately before operation or

Primocort i.v.:

II. 25—50 mg. 2 days before the operation, added to an intravenous infusion of glucose.

Polyarthritis, acute rheumatic — see Rheumatism, acute

Polyarthritis, chronic rheumatic — see Rheumatoid arthritis

Polymenorrhoea, retardation of periods

a) With a shortened proliferation phase:

Progynon B oleosum forte: *Anti-pituitary effect*

I. 5—10 mg. i. m. once or twice between the 4th and 6th days of the cycle **or**

Testoviron:

II. 5—10 mg. i. m. daily in the first 14 days after menstruation.

b) With a shortened secretory phase:

Proluton: *Substitution therapy*

I. 5—10 mg i. m. 3—4 times a week for 14 days after ovulation **or**

Duogynon:

II. From the 20th or 22nd to the 26th day of the cycle, one ampoule (20 mg. progesterone plus 2 mg. oestradiol benzoate) i. m. every other day.

Pregnancy, prolongation of — see Dystocia

Pregnancy, vomiting of — see Vomiting of pregnancy

Premature infants, rearing of

Testoviron: *Anabolic effect*

I. 4 mg. i m. daily **or**

Testoviron tablets:

II. 2—5 mg once a day crushed up in the diet.

Osteoporosis *Metabolic effect*

In both sexes:

Testoviron:

25 mg. i. m. daily and in addition

Progynon B oleosum:

1 mg. i. m. daily.

In the male.

Testoviron:

25 mg i m at first 3 times and later twice a week.

In the female:

Progynon B oleosum forte:

5 mg. i. m. 2—3 times a week.

Otosclerosis — see Ageing, hard hearing due to

Ovulation, bleeding at *Substitution therapy*

Progynon B oleosum:

5 mg. i. m. at the time of ovulation.

Ozaena

Priantin: *Pituitary therapy*

1,000 i.u. twice a week i m., possibly in combination with vitamin E.

Paget's disease *Heterosexual and anabolic effects*

In the male:

Progynon B oleosum forte:

5 mg. i. m. every other day for several weeks.

In women:

Testoviron:

25 mg. i. m. 2—3 times a week for several weeks

Testoviron tablets:

III 5 mg buccally 2—4 times a day or

Testoviron T:

IV. 10—15 drops transcutaneously 3 times a day.

Protein deficiency — see Dystrophy due to protein deficiency

Pruritus *Local effect*

In women, especially at the climacteric·

Progynon ointment:

I. 1—2 g., i. e. 6—12 cm., of ointment locally twice a day or

Progynon B oleosum:

II. 1—5 mg. i. m. 2—3 times a week.

In premenstrual pruritus.

Proluton:

5 mg. i m. 4—5 times within the last 14 days before the period begins.

In men:

Testoviron:

I. 25 mg. i. m. 2—3 times a week, later 10 mg. i m. or

Testoviron-Depot:

II Every 2—4 weeks, 50—100 mg. i. m

As after-treatment also

Testoviron tablets:

One 5 mg tablet buccally 2—3 times a day

Psoriasis, especially psoriatic arthropathy

Primocort: *Metabolic and articular effects*

5—10 mg. i. m 2—3 times a week for at least 3 weeks. In addition, large doses of vitamin C.

Primocort: *Metabolic effect*

III 10—20 mg i.m., given to the mother 1—2 hours ante partum

2.5—5 mg i.m. daily to the newborn infant from the 2nd day of life for 2 or 3 weeks.

Premenstrual symptoms (hyperoestrinism or hyperfolliculinism)

— see under the relevant symptoms; mastodynia, migraine, dysmenorrhoea, psychoses.

Prostate, carcinoma of

Anti-pituitary therapy

Progynon M:

At first, 1—2 tablets orally 3 times a day; later slow reduction in dose to 1 tablet a day (*maintenance dose*).

For after-treatment.

Progynon implants:

20 mg once or twice at intervals of 2—4 months

Prostatic hypertrophy

Progynon M: *Anti-pituitary therapy*

1—2 tablets orally daily.

In the early stages of the condition, or as preparation for operation:

Testoviron: *Raising bladder tonus*

I. At first, 25 mg i.m. daily. After improvement, 10 mg. i.m. daily or 3 times a week.

Testoviron-Depot:

II. Every 2—4 weeks, 250—100 mg. i.m.
After improvement 50 mg. i.m.

Local effect

Pyorrhoea

In both sexes:

Progynon drops:

Massage the gums twice a day with a cottonwool tampon soaked in Progynon.

Protein detoxication

Radiation sickness

Primocort:

a) As prophylaxis:

I. 2.5—5 mg. i. m.

or

II. One tablet buccally for 2 doses, shortly before and shortly after each irradiation.

b) If radiation sickness has already appeared:

I. 5 mg. i. m. daily

or

II. One tablet buccally 3—4 times a day.

Renal disease — see Nephropathy

Resistance, increase in — see Infectious diseases

Retinitis, diabetic — see Diabetic retinitis

Inhibition of mesenchymal reaction

Rheumatism, acute

ACTH "Schering A. G. Berlin":

Initial dose 60—80 i. u. daily i. m. in equal 4-hourly doses, for 4 days. From the 5th day, lowering of daily dose by 5—10 i. u. Reduced dose to be kept at same level only for 2—3 days. In many cases, transition to next lower dose possible each day.

After disappearance of clinical symptoms, *ACTH* may be discontinued. The daily dose at the end

In milder cases:

I. Begin treatment with *Primocort* in 5 mg. doses i. m. 2—3 times a week for 1—2 weeks. Further treatment with

Primocort tablets:

One tablet buccally 2—3 times a day for several weeks. In addition, vitamin C or without previous injection treatment

II. One tablet buccally 2—3 times a day for at least 3 weeks. *Additionally*, vitamin C.

Diet must always be poor in potassium. Usual local treatment should continue during hormone treatment.

Also, in women only:

Proluton:

10—20 mg daily i. m.

Psychoses

In women: see also Climacteric

Premenstrual form:

Testoluton: *Anti-oestrogen therapy*

3 ampoules (one ampoule contains 15 mg testosterone propionate plus 10 mg. progesterone) i. m. during the last 10 days before the period begins.

In men: see also Climacteric, male

Testoviron-Depot:

250 mg. i. m. every 14 days, or even more.

Pyometra

Progynon B oleosum forte:

5 mg. i. m. for 3 doses at 2—3 day intervals.

Pyorrhoea *Local effect*

In both sexes·

Progynon drops:

Massage the gums twice a day with a cottonwool tampon soaked in Progynon.

Radiation sickness *Protein detoxication*

✓ *Primocort:*

a) As prophylaxis.

I. 2.5—5 mg. i. m. or

II. One tablet buccally for 2 doses, shortly before and shortly after each irradiation.

b) If radiation sickness has already appeared.

I 5 mg. i. m. daily or

II. One tablet buccally 3—4 times a day.

Renal disease — see Nephropathy

Resistance, increase in — see Infectious diseases

Retinitis, diabetic — see Diabetic retinitis

Rheumatism, acute *Inhibition of mesenchymal reaction*

ACTH "Schering A.G. Berlin":

Initial dose 60—80 i. u. daily i. m. in equal 4-hourly doses, for 4 days. From the 5th day, lowering of daily dose by 5—10 i u. Reduced dose to be kept at same level only for 2—3 days. In many cases, transition to next lower dose possible each day.

After disappearance of clinical symptoms, *ACTH* may be discontinued. The daily dose at the end

of treatment may be of the order of 7.5—5 i. u. Tapering off need not be so carefully done as with rheumatoid arthritis. Duration of treatment between 10 and 30 days.

Rheumatoid arthritis, primary and secondary

ACTH "Schering A.G. Berlin": Inhibition of mesenchymal reaction

Initial dose 50—80 i. u. daily i. m., according to the severity of the condition and its duration, divided into 6 equal 4-hourly doses, for 5—7 days. If significant improvement appears earlier, a start may be made with reducing the dose. After appearance of improvement, lowering of daily doses by 10—15 i. u. at a time, with simultaneous transition to 6-hourly doses. Lower dose to be maintained on each occasion for 3—5 days, before the next reduction. Any larger reduction must be absolutely avoided!

Aim of lowering dosage: Determination of a minimal therapeutic maintenance dose (usually between 10 and 30 i. u. daily). With the latter, further treatment for 8—14 days according to the condition, with increase in injection intervals to 6—8 hours.

Towards the end of the course, further reduction in dosage from day to day, to a total daily dose of 7.5—5 i. u., now divided only into two individual doses daily.

Finally, tapering off to single daily doses of 5 or 2.5 i. u. i. m. with increase in injection intervals to 2—3 days. Duration of a course between 4 and 8 weeks.

If recurrence, repeat a shorter course of ACTH, possibly with smaller doses.

Rosacea and rosacea keratitis

Primocort:

I. 5—10 mg. i. m. 2—3 times a week for at least 3 weeks or

Primocort tablets:

II. Begin treatment with at least 5 doses of 5—10 mg. *Primocort* i m. during 7—10 days. Continue treatment with one tablet buccally 2—3 times a day for 4—6 weeks.

Salpingitis, chronic

Progynon B oleosum forte:

5 mg. i. m. for 5 doses every 5th day at the conclusion of a period. Cyclical repetition.

Sexual neurasthenia — see Climacteric, male

Shock, operative — see Operative shock

Simmonds's cachexia

ACTH "Schering A.G. Berlin": *Substitution therapy*

I. Initial dose 60—80 i. u. daily i. m., in equal single doses at 4-hourly intervals, for 5—8 days.

Then as in rheumatoid arthritis, gradual lowering of dosage and determination of a minimum but still therapeutically effective dosage for maintenance. Further treatment with the latter for 3—4 weeks.

Finally, towards the end of treatment, gradual tapering off. Conclusion of the course with daily doses of 5—2.5 i. u., and lengthening of the intervals between injections to 2—3 days. Duration of course 6—8 weeks.

Priantin: *Substitution therapy*

II. In w o m e n : 1,000 or 5,000 i. u. 2—3 times a week i. m., alternating every other week. If periods present, injections in the first two weeks of the cycle; repetition only after the next period.

In m e n : 5,000 i. u. 2—3 times a week i. m. in injection series each of 10 with interpolation of rests of several weeks. Possible combination with *Testoviron:* 10 mg. i. m. 3 times a week.

Primothyron: *Substitution therapy*

III. 500 guinea-pig units daily i. m. until the general condition improves.

Primocort: *Substitution therapy*

IV. 5—10 mg. i. m. daily, together with the usual hormone therapy.

Sterility

In w o m e n .

a) With underdevelopment of the genitals:

Progynon B oleosum: *Substitution therapy*

1 or 5 mg. i. m for 4 or 5 doses within the first 14 days after menstruation Followed by

Proluton:

10 mg i. m. 3—5 times within the last 10 days before the next period.

b) With normal genitalia, especially if the corpus luteum phase is shortened:

Proluton: *Substitution therapy*

I. 10 mg. i m 3—5 times within the last 10 days before the next period or

Duogynon:

II. From the 20th or 22nd to the 26th day of the cycle, one ampoule (20 mg. progesterone plus 2 mg. oestradiol benzoate) i. m every other day, as in polymenorrhoea **or**

Primogonyl: *Stimulation therapy*

III. 500 i u. 3 times a week i m from the 14th day of the cycle to the beginning of the period

Further suggestions if genitalia are normal

Progynon dragees or dragees forte ·

IV One dragee buccally 3 times a day **or**

Progynon drops ·

V *10 drops perlingually 3 times a day*

c) With an anovulatory cycle.

Priantin:

1,000—5,000 i. u. 2—3 times a week i. m. in the first two weeks of the cycle Followed by

Primogonyl:

1,000 i. u., i. m., on the 13th, 15th and 17th days of the cycle.

d) With a shortened secretory phase – see Polymenorrhoea.

In men.

a) Azoospermia:

Testoviron: *Stimulation therapy*

10 mg i m 2—3 times a week. In addition

Priantin:

1,000—5,000 i u once or twice a week i. m. Possibly supplemented by vitamin E.

Priantin: *Substitution therapy*

II. In w o m e n : 1,000 or 5,000 i. u. 2—3 times a week i. m., alternating every other week. If periods present, injections in the first two weeks of the cycle; repetition only after the next period.

In m e n : 5,000 i. u. 2—3 times a week i. m. in injection series each of 10 with interpolation of rests of several weeks. Possible combination with *Testoviron:* 10 mg. i. m. 3 times a week.

Primothyron: *Substitution therapy*

III. 500 guinea-pig units daily i. m. until the general condition improves.

Primocort: *Substitution therapy*

IV. 5—10 mg. i. m daily, together with the usual hormone therapy.

Sterility

In w o m e n :

a) With underdevelopment of the genitals:

Progynon B oleosum: *Substitution therapy*

1 or 5 mg. i. m. for 4 or 5 doses within the first 14 days after menstruation. Followed by

Proluton:

10 mg i. m. 3—5 times within the last 10 days before the next period.

b) With normal genitalia, especially if the corpus luteum phase is shortened:

Proluton: *Substitution therapy*

I. 10 mg. i. m. 3—5 times within the last 10 days before the next period or

Thrombosis and embolism, prophylaxis of *Metabolic effect*

Primothyron:

500 guinea-pig units daily i. m. for 3 days before operation

Thyroid, assessment of function with radio-iodine

Primothyron: *Testing iodine-storage capacity*

Normally 8 hours after injection of 500 guinea-pig units i. m. there is increased storage of radio-iodine in the thyroid tissue. The state of thyroid function can be assessed from the degree of iodine uptake or its absence.

Thyroid, malignant tumours treated with radio-iodine

Primothyron: *Increasing iodine-storage capacity*

500 guinea-pig units i. m. on several occasions can increase the storage capacity of malignant thyroid tumours and their metastases for radio-iodine. The dosage is quite individual, according to the case.

Ulcer, gastric and duodenal

In women:

Progynon B oleosum: *Promotion of circulation*

1 mg. i. m. daily in the first week,
every other day in the 2nd week,
every third day in the 3rd and 4th weeks.

In men:

Progynon B oleosum:

1 mg. i. m. daily in the first week,
every other day in the 2nd week,
every third day in the 3rd and 4th weeks.
Together with

b) *Necrospermia:*

Testoviron:

25 mg. i. m. 2—4 times a week.

c) Oligospermia:

Testoviron:

I. 25 mg. i. m. twice a week. Simultaneously or following this

Priantin:

1,000 i. u. 2—3 times a week i. m., to a total of 10,000 i. u. Repetition after several weeks.

Testoviron-Depot:

II. 100 mg. i. m. every 2—4 weeks.

Thinness

Primocort: *Metabolic effect*

I. 5—10 mg. i. m. daily for several weeks or

Priantin: *Stimulation therapy*

In women:

II In the first two weeks of the cycle, 1,000 or 5,000 i. u. 2—3 times a week, in injection series of 10, with interpolation of several weeks' rests or

In men

III 1,000 or 5,000 i. u. 2—3 times a week i. m. for 3—5 weeks this may be repeated several times with 2—3 week intervals or

In women

Progynon B oleosum.

IV. 1 mg. i. m. every 4 days during the first half of the cycle

In men see Dystrophy due to protein deficiency

Testoviron:

V 10 mg i m twice a week

Thrombosis and embolism, prophylaxis of *Metabolic effect*

Primothyron:

500 guinea-pig units daily i m. for 3 days before operation.

Thyroid, assessment of function with radio-iodine

Primothyron: *Testing iodine-storage capacity*

Normally 8 hours after injection of 500 guinea-pig units i. m. there is increased storage of radio-iodine in the thyroid tissue. The state of thyroid function can be assessed from the degree of iodine uptake or its absence.

Thyroid, malignant tumours treated with radio-iodine

Primothyron: *Increasing iodine-storage capacity*

500 guinea-pig units i. m. on several occasions can increase the storage capacity of malignant thyroid tumours and their metastases for radio-iodine. The dosage is quite individual, according to the case.

Ulcer, gastric and duodenal

In women:

Progynon B oleosum: *Promotion of circulation*

1 mg. i. m. daily in the first week,
every other day in the 2nd week,
every third day in the 3rd and 4th weeks.

In men

Progynon B oleosum:

1 mg. i. m. daily in the first week,
every other day in the 2nd week,
every third day in the 3rd and 4th weeks.
Together with

Testoviron:

25 mg. twice a week in the 1st and 2nd weeks,
10 mg. i. m. twice a week in the 3rd and 4th weeks.

In both sexes:

Primocort: *Local effect*

10—20 mg. i. m. daily or every other day, to a total of about 15 injections.

Primocort tablets:

For prevention of recurrence after injection treatment, one tablet buccally 2—3 times a day for at least 3 weeks.

Tuberculosis *Substitution therapy*

Primocort:

I. 10 mg. i. m. 2—3 times a week, together with specific therapy *or*

Primocort tablets:

II. One tablet buccally 3 times a day for several weeks

or

III. Further treatment with 1 tablet buccally 2—3 times a day after previous injection treatment for at least 14 days.

Ulcer of leg — see Circulatory disturbances

Uterus, carcinoma of — see Breast, carcinoma of

Vaginal hypoplasia or atresia *Peripheral effect*

For postoperative treatment:

Progynon ointment:

I. For tampon or bougie treatment.

Progynon implants:

II 10 or 20 mg locally under the mucosa.

Vaginitis, senile atrophic (Colpitis) *Substitution therapy*

Progynon B oleosum:

I. 1 mg. i. m. 1—2 times a week.

Progynon ointment:

II. For tampon treatment or

Progynon dragees:

III One dragee buccally 3 times a day often suffices or

Progynon drops:

IV 10 drops perlingually 3 times a day

Vegetative dystonia *Stabilization of circulation, toning up of the autonomic nervous system*

Primocort tablets:

One tablet buccally 2—3 times a day for at least 4—6 weeks. According to response after 2—3 weeks, daily dose may be lowered to one tablet.

Vomiting of pregnancy

Primocort: *Substitution therapy*

5—10 mg. i m. daily

In mild and moderately severe cases

Primocort:

I Begin treatment with at least 5—10 mg i. m. for 4 doses, continue as in II or

Primocort tablets:

II One tablet buccally 1—3 times a day.

Therapy should be continued for a while after vomiting has ceased.

ACTH "Schering A. G. Berlin": *Stimulation therapy*

In severe cases, the vomiting can be cut short by giving 25 i. u. daily i. m., divided into 5 equal doses. Continue *ACTH* treatment only for 2 or 3 days, then continue with Primocort as above.

Vulvo-vaginitis, gonococcal in children

Progynon B oleosum:

A single dose of 1 mg. i. m.; after 24 hours, penicillin treatment.

Wound healing, promotion of, in large soft-part wounds

Primothyron: *Metabolic effect*

500 guinea-pig units i. m. 2—3 times a week.

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